A Dissertation on

A STUDY ON LIPID PROFILE AS AN INDICATOR OF SEVERITY IN CIRRHOSIS OF LIVER

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CERTIFICATE - II

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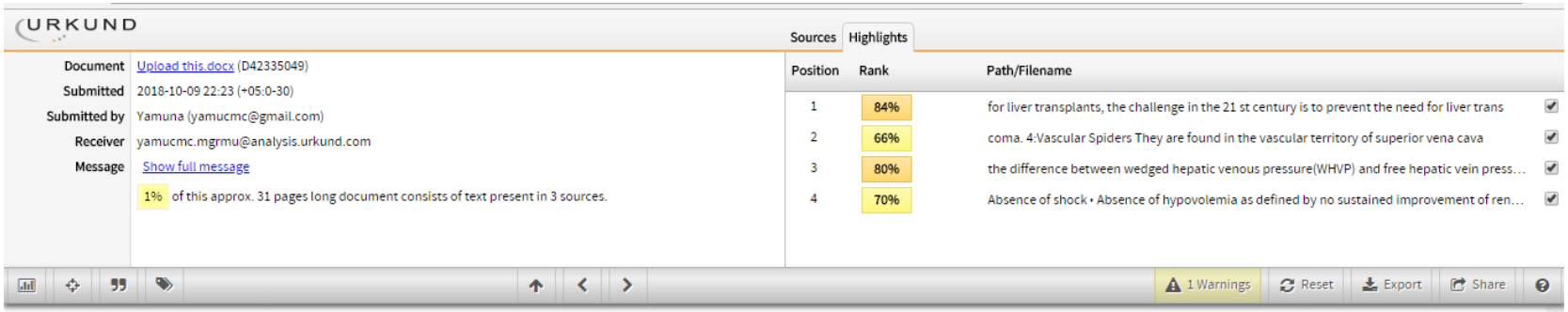

INTRODUCTION Cirrhosis derives from the Greek word meaning "tawny" and it was initially used to describe the gross and microscopic appearance of the chronically diseased and physiologically burned out and dysfunctional liver. Cirrhosis is fourth leading cause of death among Asian males. Cirrhosis of liver is one of the commonest diseases which physicians encounter both at primary as well as tertiary care level. Cirrhosis is a degenerative condition of the liver in which normal hepatic tissue is replaced by microscopically abnormal structures, which eventually impair liver synthetic as well as excretory function. Liver cirrhosis represents the advanced stage of hepatocellular injury caused by chronic liver diseases such as infectious causes like hepatitis, alcoholic liver disease and various other causes and may gradually end in hepatic failure and hepatocellular carcinoma. Cirrhosis is an increasing cause of morbidity and mortality in more developed countries and also developing countries, being the 14th most common cause of death worldwide but fourth in central Europe. Increasingly, cirrhosis has been seen to be not a single disease entity, but it can be subclassified into distinct clinical prognostic stages, with 1-year mortality ranging from 1% to 57% depending on the stage. The new concept in management of patients with cirrhosis should be prevention and early

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many patients with cirrhosis as possible. Chronic liver disease (CLD) affects more than 29 million people in Europe [1] and over 300 million people worldwide. Over time, extracellular fibrotic tissue develops which accumulates in the liver as a result of chronic injury, progressively leading to fibrous septa that prevent normal hepatic tissue oxygenation and blood exchange to the liver parenchyma. This late stage, featuring marked liver anatomical changes, including extinction of hepatocytes, micro- and macrovascular remodeling, angioneogenesis, nodule formation and development of portosystemic shunts, is termed 'cirrhosis'2

DECLARATION

I solemnly declare that the dissertation titled **"A STUDY ON LIPID PROFILE AS AN INDICATOR OF SEVERITY IN CIRRHOSIS OF LIVER"** was done by me from JULY 2017 to JUNE 2018 under the guidance and supervision of **Prof. DR. K. SIVAKUMAR, M.D.** This dissertation is submitted to **The Tamil Nadu Dr. M.G.R. Medical University** towards the partial fulfillment of the requirement for the award of MD Degree in General Medicine (Branch I).

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Dr. J. YAMUNA

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I. INTRODUCTION

Cirrhosis derives from the Greek word meaning “tawny” and it was initially used to describe the gross and microscopic appearance of the chronically diseased and physiologically burned out and dysfunctional liver. Cirrhosis is fourth leading cause of death among Asian males. Cirrhosis of liver is one of the commonest diseases which physicians encounter both at primary as well as tertiary care level. Cirrhosis is a degenerative condition of the liver in which normal hepatic tissue is replaced by microscopically abnormal structures, which eventually impair liver synthetic as well as excretory function.

Liver cirrhosis represents the advanced stage of hepatocellular injury caused by chronic liver diseases such as infectious causes like hepatitis, alcoholic liver disease and various other causes and may gradually end in hepatic failure and hepatocellular carcinoma. Cirrhosis is an increasing cause of morbidity and mortality in more developed countries and also developing countries, being the 14th most common cause of death worldwide but fourth in central Europe. Increasingly, cirrhosis has been seen to be not a single disease entity, but it can be subclassified into distinct clinical prognostic stages, with 1-year mortality ranging from 1% to 57% depending on the stage. The new concept in management of patients with cirrhosis should be prevention and early intervention to stabilize disease progression and to avoid or delay clinical decompensation and the need for liver transplantation. The challenge in the 21st century is to prevent the need for liver transplantation in as many patients with

cirrhosis as possible. Chronic liver disease (CLD) affects more than 29 million people in Europe [1] and over 300 million people worldwide. Over time, extracellular fibrotic tissue develops which accumulates in the liver as a result of chronic injury, progressively leading to fibrous septa that prevent normal hepatic tissue oxygenation and blood exchange to the liver parenchyma. This late stage, featuring marked liver anatomical changes, including extinction of hepatocytes, micro- and macrovascular remodeling, angioneogenesis, nodule formation and development of portosystemic shunts, is termed 'cirrhosis'[2]. Mortality in CLD is primarily due to complications of liver cirrhosis and hepatocellular carcinoma (HCC), which is more prevalent in patients with cirrhosis when compared to general population. The term 'advanced chronic liver disease' (ACLD) ranging from severe fibrosis to fully developed cirrhosis.

Reduced exposure to hepatitis infections also attributed to the declining in mortality rate from cirrhosis since 70's. Because of doubling of alcoholic incidence, Scotland had high cirrhotic mortality. Worldwide cirrhosis contributes 8 lakh deaths because of irreversible damage to liver. Exact incidence rates are difficult to estimate as cirrhosis remains unnoticed until end-stage disease has encountered. Although several treatments attempt to restrict further disease progression and reduce complications of cirrhosis, liver transplantation is the only line of permanent management option available when the most of the hepatocytes fail to function But even after liver transplantation, long-term survival of the patient is not guaranteed as graft rejection may occur. Because of the risk of relapse, patients with alcoholic cirrhosis are only eligible

for a orthotopic liver transplantation after attaining 6 months of abstinence from alcohol.

Lipids are one of the necessary components of cell wall and also which control cellular functions and homeostasis. Liver plays an essential role in lipid metabolism, as it is the major site of converting excess carbohydrate into triglyceride and fatty acids several stages of lipoprotein synthesis and transportation. The liver synthesizes large quantities of cholesterol and phospholipids. Majority of endogenous cholesterol is synthesized in the liver and its excretion by lipoprotein remnants. Synthesis and metabolism of cholesterol is impaired in chronic liver disease. This eventually results in decrease in plasma levels. High density lipoprotein (HDL) cholesterol and its major Apo lipoproteins have been shown to be reduced in cirrhosis, because of the severe metabolic derangement as also the serum levels of low-density lipoprotein (LDL) cholesterol.

Hence this study aims at studying the changes in lipid profile in Cirrhosis, Thereby recommending assessment of the need for lipid profile in all the patients as a prognostic indicator of severity of liver cell injury.

II. AIMS AND OBJECTIVES

1. To assess the lipid profile abnormalities in patients with cirrhosis of liver.
2. To correlate with the severity of cirrhosis.

III. REVIEW OF LITERATURE

HEPATIC ANATOMY

The term liver in Greek, is the largest parenchymal organ, weighting approximately 1.2 - 1.5 kg and comprises one fifth of total body weight. It is relatively larger during infancy weighing one eighteenth of the birth weight. This is due mainly to left lobe of liver. The liver receives up to 25% of the total cardiac output[1], indicating its major role in the metabolism like synthetic, excretory and detoxifying functions and its necessity for survival. Various metabolic and detoxifying functions are carried out by the liver. As liver is the major site of glycogenolysis and gluconeogenesis, the liver is involved in maintenance of blood glucose level during fasting states. Other metabolic functions include the breakdown of proteins and lipids, gluconeogenesis from other substrates and the synthesis of cholesterol and triglycerides. The most prominent detoxifying function of the liver is the biotransformation of lipophilic substances (Medication, nutrition additives, steroid hormones etc.) to increase the way for excretion.

Liver produces daily about 500 ml of bile, and between 250 to 500 mg of bile acids which either lost directly through fecal route or will be temporarily stored in the gallbladder. Liver is responsible for detoxifying the toxins via three mass transport system namely blood, lymph, bile.

HEPATIC BLOOD SUPPLY

Like few other organs in the body, the liver's vascular system is composed of two supplying blood vessels, the hepatic artery and the portal vein. Both vessels ramify at the level of the liver hilum i.e porta hepatis in branches towards the right and left lobe. The hepatic artery provides the liver with oxygenated blood which is a branch of coeliac axis, accounting for nearly 20% of the total blood flow to the liver.

Fig: 1. Anatomy of Liver

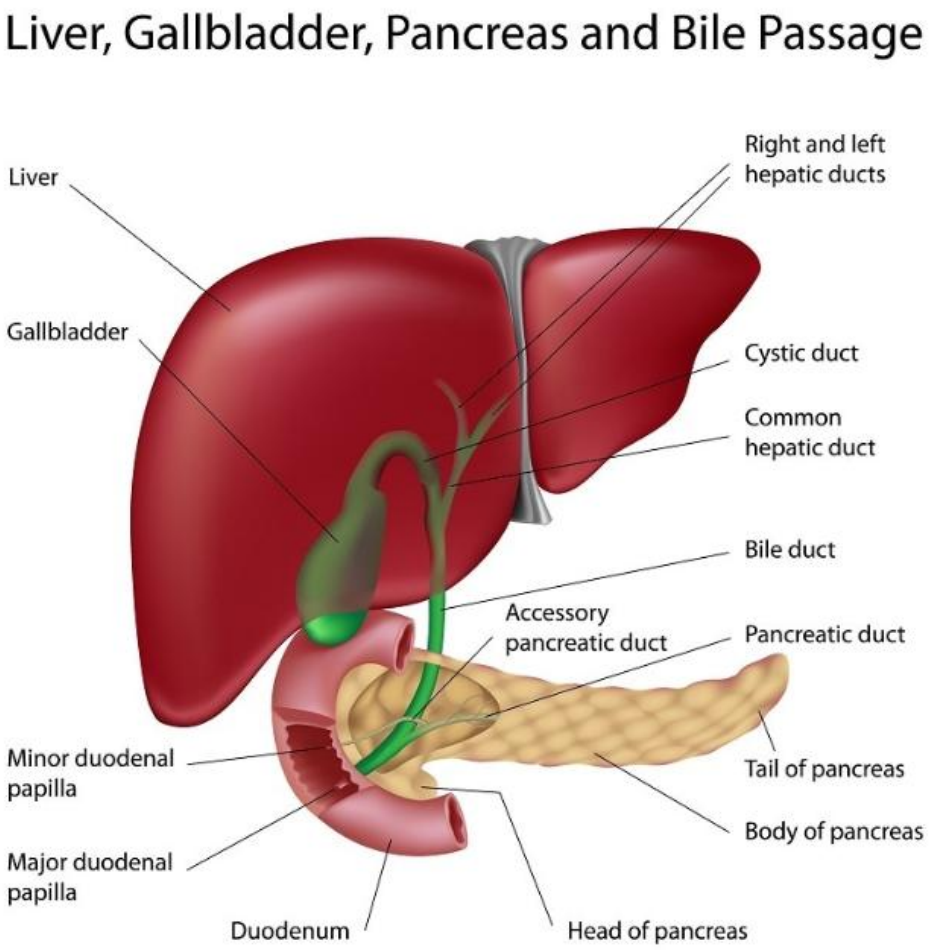
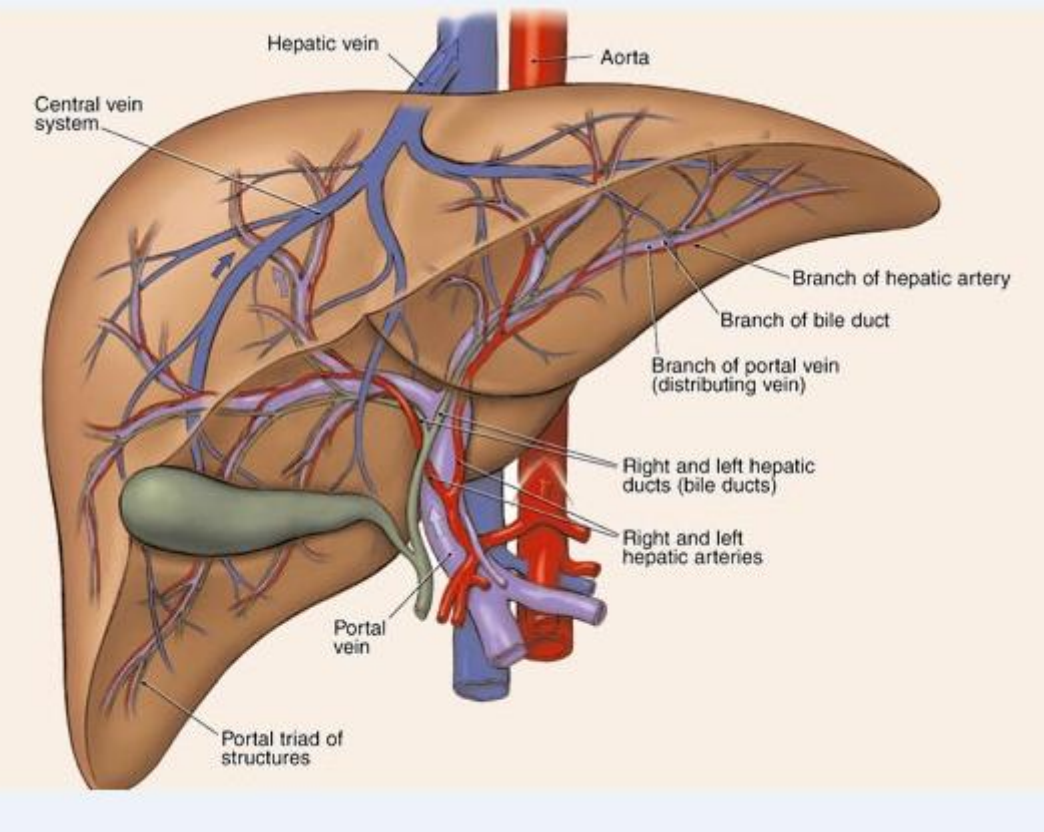


Fig 2: Blood supply of Liver



The remaining blood supply of about 80% is delivered by the portal vein and contains nutrient enriched but venous blood from the intestines and spleen. Venous drainage of the liver is assured via the hepatic veins. When the blood supply to liver is compromised with reduced portal flow, the hepatic blood flow will increase to maintain the circulation to liver. The mechanism depends on local depletion of adenosine, resulting in either arterial dilation or contraction[2] .

The hepatic biliary tree counts two hepatic bile ducts emerging from the liver. Both hepatic bile ducts join together at hilum to form common bile duct, which transports the bile[1]. The liver also produces enormous amount of lymph, which is mainly produced at a cellular level (The sinusoids). So the result is, the liver has a deep lymphatic network for drainage of the lymph directed towards

the heart[3]. When sinusoidal pressure raises lymph production in Disse's space is increased which plays a vital role in ascites formation in case of portal hypertension.

FUNCTIONAL ANATOMY

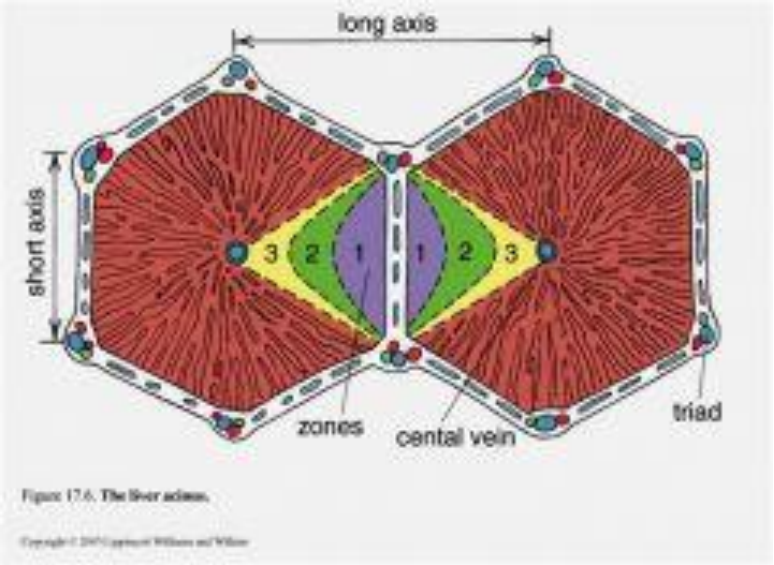
HEPATIC LOBULE

Functional anatomy is now recognized only based on vascular and biliary anatomy. The liver lobes are classified by 'Couinaud classification', composed of repetitive anatomical units called hepatic lobules [4]. Lobes consist of eight segments with I-IV segments in left lobe and V-VIII segments in right lobe. The hepatic lobules resemble the shape of hexagonal prisms, which are introduced by Kiernan in 1833. The different vessel systems are separated by approximately 0.5 mm (5). Portal triads contain the portal vein, hepatic artery and bile duct (portal venule, hepatic arteriole and a bile ductile).

HEPATIC ACINUS

When looking from a metabolic perspective to the microcirculation, one of the proposed functional units is the hepatic acinus which is envisaged by Rappaport (6). The acinus is centered on a line connecting two terminal portal tracts with its terminal branch of portal vein, hepatic artery and bile duct and is divided in different metabolic zones.

Fig: 3. Hepatic Acinus



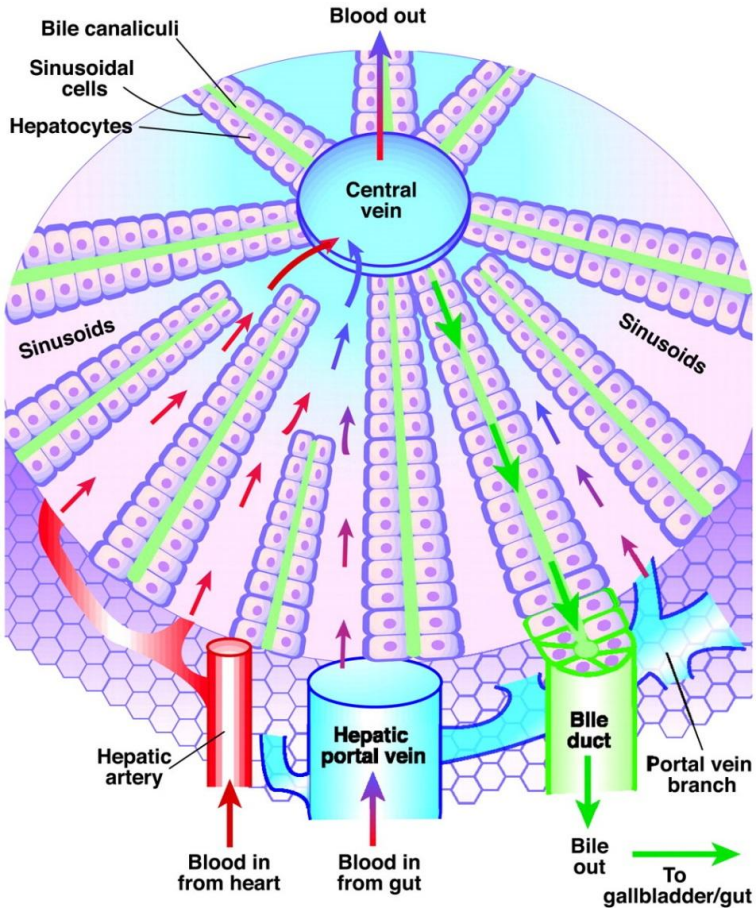
The periportal zone I is situated closest to the arriving oxygenated blood flow. Therefore, zone I hepatocytes are specialized in oxidative liver functions (e.g. gluconeogenesis). Bridging necrosis may extend from periphery (zone I) to zone 3. The centrilobular zone III, on the other hand, receives blood of lesser quantity and thus may suffer most from ischemic injury whether viral, toxic, or anoxic. This region is vulnerable to ischemic damage, it still considerably helps in detoxification of blood. Hepatocytes contained within zone I survive longer because of enormous blood supply and it is the basis for liver regeneration after partial hepatectomy. This well architecture regenerative response of the hepatocytes helps them restore lost tissue up to two third of its total mass, while simultaneously performing vital functions to maintain the body homeostasis[7&5].

SINUSOIDAL CELLS

A liver sinusoid is a type of capillary called as, sinusoidal capillary or discontinuos capillary that is similar to fenestrated capillary which contains mixed blood from portal vein and hepatic artery. The sinusoidal cells (endothelial cells, Kupffer cells, hepatic stellate cells, pit cells) form a functional and histological unit together with sinusoidal aspect of hepatocyte.

Plasma constituents gain access to the sub endothelial space of Disse due to fenestrae (approximately 0:15µm in diameter) acting as transport pores in the continuous endothelial lining. They act as a biofilters and transport between sinusoidal blood and plasma within the space of Disse.

Fig: 4. Hepatic acinus - histology



The perisinusoidal space of Disse (named after German anatomist Joseph Disse) is situated between the hepatocytes and the sinusoids. Fenestrae have a dynamic cytoskeleton to preserve and control their size, which can be influenced by various factors like alcohol, nicotine, etc. the particle greater than 0.2 um in diameter which includes large triglyceride rich parent chylomicrons will not pass. A graded barrier is formed, retaining the macromolecules like proteins and RBC's within the vascular space. In this way the fenestrae have an important role in chylomicron and lipoprotein metabolism. Pinocytosis, carried out by the endothelial cells, enables the clearance of other vital (macro) and small particles and denatured collagen from the circulation. The extracellular matrix may alter the sinusoidal capacity which is normally present, to sieve the blood particles by influencing the diameter of the endothelial fenestrae[5].

CIRRHOSIS

Cirrhosis results from different mechanisms of liver injury that lead to necroinflammation and fibrogenesis; histologically it is characterized by diffuse nodular regeneration surrounded by dense fibrotic septa with subsequent parenchymal extinction and collapse of liver architecture structures, together causing extensive distortion of hepatic vascular architecture. This distortion results in increased resistance to portal blood flow and hence in portal hypertension and in hepatic synthetic and excretary dysfunction. Clinically, cirrhosis has been regarded as an end-stage disease that invariably leads to death.

The liver is an organ that can withstand a certain degree of damage, because of its remarkable capacity to regenerate after injury either chemically or surgically. As little as 25% of the original liver mass can regenerate back to its full size. However, in case of cirrhosis, repeated insults to hepatocytes diffusely causing inflammatory changes which result in cell necrosis. As a response to process of necrosis, repair by fibrogenesis is activated to cooperate in the wound healing process. Hyperplasia of the surviving cells eventually occurs along with fibrosis leading to the formation of hepatocellular nodules. As hepatocyte injury sets in, further deterioration in hepatic functions occur. Cirrhosis tends to get worse by time and may even become life threatening.

EPIDEMIOLOGY

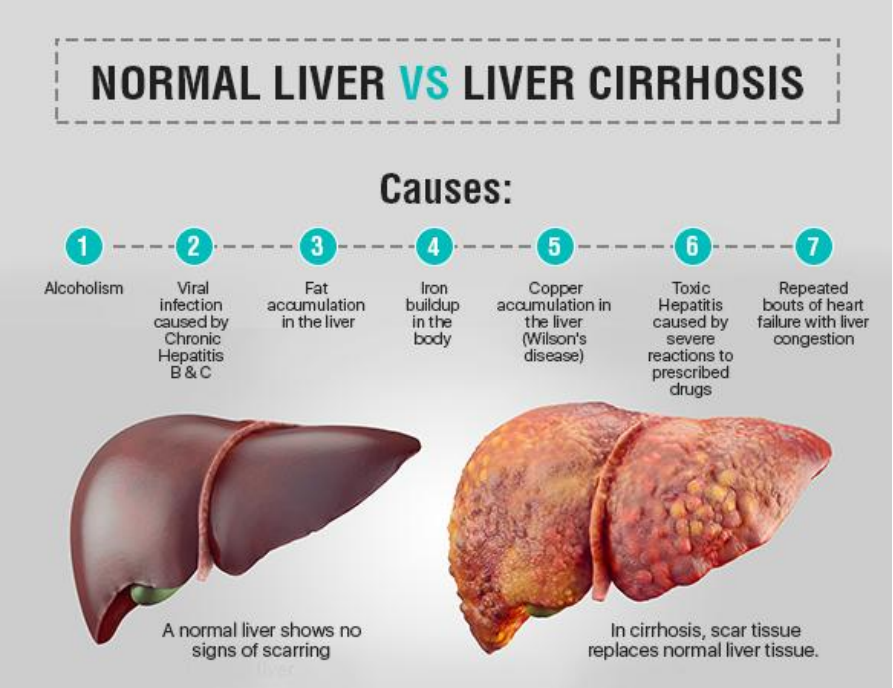
Cirrhosis is an increasing cause of morbidity and mortality in most of the developed countries. It is the 14th most common cause of death in adults worldwide but the fourth in central Europe; it results in 1•03 million deaths per year worldwide,8 170 000 per year in Europe,9 and 33 539 per year in the USA.10 Cirrhosis is the main indication for 5500 liver transplants each year in Europe.9 The main causes in more developed countries are infection with hepatitis C virus, alcohol misuse, and, increasingly, non-alcoholic liver disease; infection with hepatitis B virus is the most common cause in sub-Saharan Africa and Asia. The prevalence of cirrhosis is difficult to assess and probably higher than reported, because the initial stages are asymptomatic so it is undiagnosed. Prevalence was estimated at 0•3% and the annual incidence was 15•3–132•6 per 100 000 people in studies in the UK and Sweden.

Cirrhosis is characterized by fibrosis and regenerative nodules.[9] Two important components of cirrhosis are, the connective tissue septa formation and regenerative nodules, account for the main pathophysiology of cirrhosis, irrespective of its etiologic starting point. Though the term cirrhosis is assumed to be irreversible, the prior stage fibrogenesis found to be reversible. Treating the underlying etiology and also with antifibrotic agents help in regression of cirrhosis stated in few studies.

ETIOLOGY

Cirrhosis is defined as widespread fibrosis and nodule formation. In contrast Congenital hepatic fibrosis results in fibrosis without nodules. Partial nodular transformation is not a cirrhosis per se since it consists of nodules without fibrosis. The most common diseases lead to cirrhosis include chronic viral hepatitis, non-alcoholic fatty liver disease and chronic autoimmune biliary disease[10]. Alcoholic liver disease and hepatitis C are the predominant causes of cirrhosis in Western and European countries, whereas the prevalence of hepatitis B-induced cirrhosis is vastly increasing in developing countries. Age, sex, body mass index, alcohol consumption and genetic factors are often the confounding factors which interact with the preexisting cause. Alcohol consumption, for instance, may “add fuel to the fire” hastens the disease progression in HBV/HCV infections.

Fig: 5. Causes of Liver cirrhosis



The following are various causes of Cirrhosis:

- **Alcoholic liver disease**
- **Non alcoholic:**
- Viral hepatitis (A, B, C, D, E and G)
- NASH
- **Metabolic causes**
- Haemochromatosis
- Wilson’s disease
- Alpha 1 - antitrypsin deficiency
- Type IV glycogen storage diseases
- Galactosaemia
- Tyrosinaemia

Autoimmune

- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Budd – Chiari syndrome
- Heart failure- cardiac cirrhosis
- Autoimmune hepatitis
- **Toxins and drugs** e.g. methotrexate and amiodarone

PATHOGENESIS

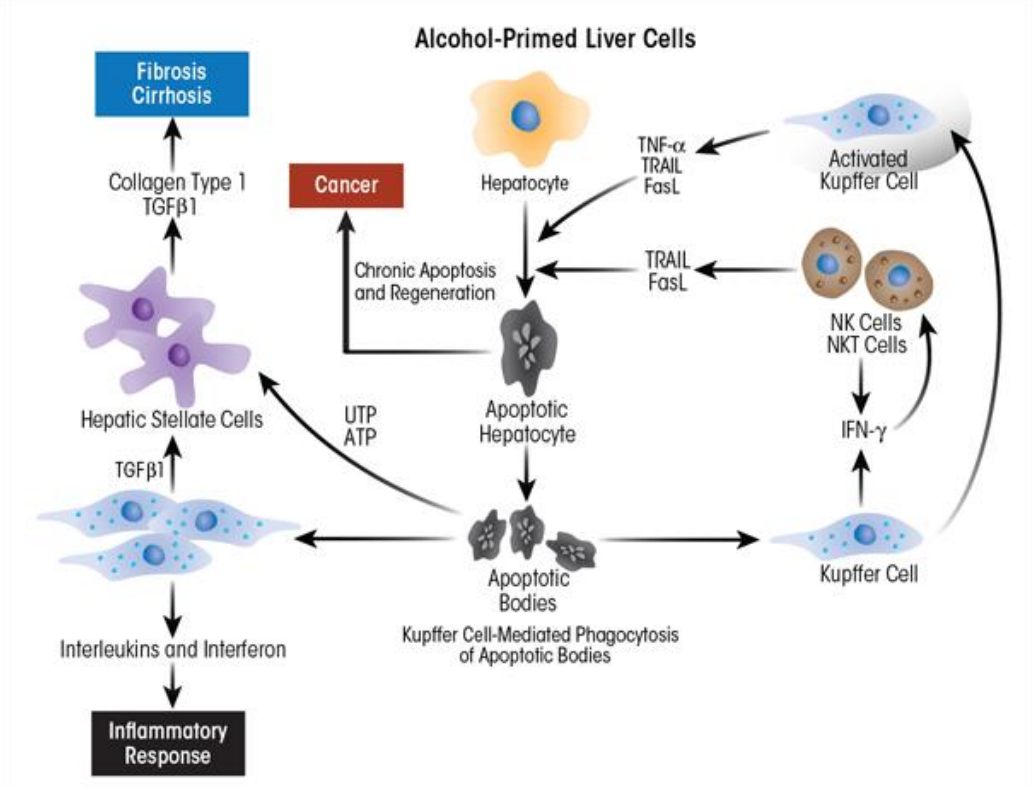
FIBROGENESIS

Fibrogenesis is a natural wound healing response in injured tissue. Fibrous scar connective tissue is produced to limit and encapsulate the damaged area. Sustained signals in response to repetitive hepatocellular injury result in excessive formation of scar tissue. Persistent accumulation of fibrosis can eventually lead to nodule formation which eventually cause the development of cirrhosis [13,15].

Normal liver has a connective tissue matrix which includes type IV collagen, glycoproteins and proteoglycans. In case of hepatic injury, there occurs eightfold increase in extracellular matrix. The causative agent of hepatic injury can regulate the progression of fibrosis, as in congestive heart failure the fibrosis occurs in zone 3 and in zone 1 in bile duct obstruction and congenital hepatic fibrosis. In addition, factors including alcohol consumption, male gender and

elderly age as seen earlier are all associated with 'rapid fibrosers'. Genetic determinants will also contribute to variable progression Rates[5].

Fig. 6. Pathogenesis of liver cirrhosis



The transition from chronic liver disease to cirrhosis involves

- inflammation
- activation of hepatic stellate cells with ensuing fibrogenesis
- angiogenesis
- parenchymal extinction lesions caused by vascular occlusion

This process leads to pronounced hepatic microvascular changes, characterized by sinusoidal remodelling (extracellular matrix deposition from proliferating activated stellate cells resulting in capillarization of hepatic sinusoids), formation of intrahepatic shunts (due to angiogenesis and loss of

parenchymal cells) and hepatic endothelial dysfunction. The endothelial dysfunction is characterized by insufficient release of vasodilators, of which the most important is nitric oxide. Release of nitric oxide is inhibited by low activity of endothelial nitric oxide synthetase (as a result of insufficient protein-kinase-B-dependent phosphorylation, lack of cofactors, increased scavenging resulting from oxidative stress and high concentrations of endogenous inhibitors of nitric oxide), with concomitant increased production of vasoconstrictors (mainly adrenergic stimulation and thromboxane A2, but also activation of the renin-angiotensin system, antidiuretic hormone, and endothelins).[13]

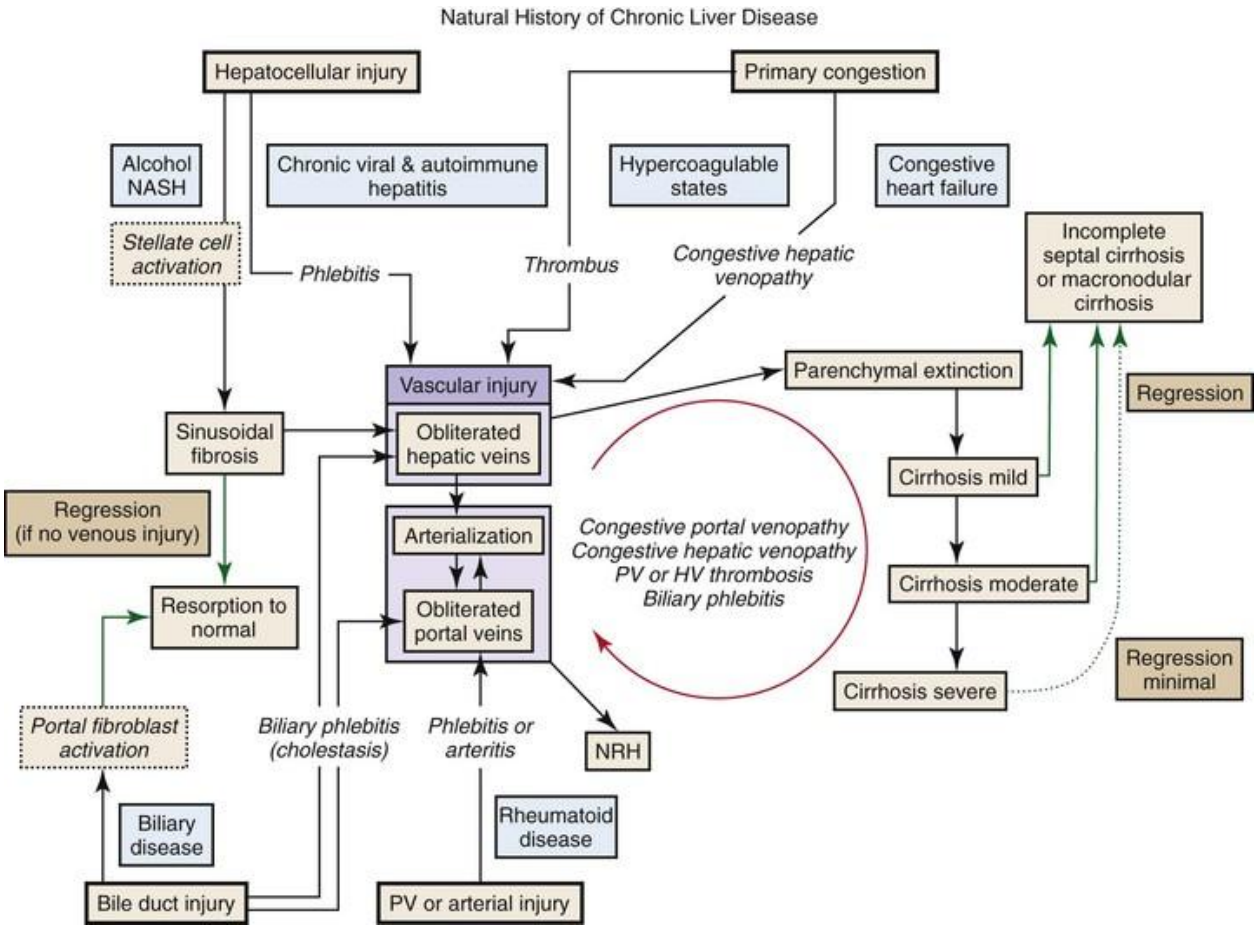
Increased hepatic resistance to portal blood flow is the primary factor increasing portal pressure in cirrhosis. It results from the combination of structural disturbances associated with advanced liver disease (accounting for about 70% of total hepatic vascular resistance) and of functional abnormalities leading to endothelial dysfunction and increased hepatic vascular tone; portal pressure could perhaps therefore be decreased by 30% if this functional abnormality were antagonised. The molecular mechanisms of these abnormalities are being delineated and represent new targets for therapy. Splanchnic vasodilation with an ensuing increase in the inflow of blood into the portal venous system contributes to aggravate the increase in portal pressure.

Splanchnic vasodilation is an adaptive response to the changes in intrahepatic haemodynamics in cirrhosis; its mechanisms are directly opposite to those of the increased hepatic vascular tone. Because of this opposition, attempts to correct portal hypertension by acting on hepatic resistance or portal blood

inflow should be ideally based on strategies acting as selectively as possible on the intrahepatic or the splanchnic circulation. In advanced cirrhosis, splanchnic vasodilation is so intense as to determine a hyperdynamic splanchnic and systemic circulation, which together with portal hypertension has a major role in the pathogenesis of ascites and hepatorenal syndrome. Systemic vasodilation further causes pulmonary ventilation/perfusion mismatch that in severe cases leads to hepatopulmonary syndrome and arterial hypoxaemia.

Portopulmonary hypertension is characterized by pulmonary vasoconstriction, which is thought to be due to endothelial dysfunction in the pulmonary circulation. Formation and increase in size of varices is driven by anatomical factors, increased portal pressure and collateral blood flow, and by angiogenesis dependent on vascular endothelial growth factor, all of which contribute to variceal bleeding. Dilation of gastric mucosal vessels leads to portal-hypertensive gastropathy. In addition, the shunting of portal blood to the systemic circulation through the portosystemic collaterals is a major determinant of hepatic encephalopathy, of decreased first-pass effect of orally administered drugs, and of decreased reticulo-endothelial system function. However, capillarisation of sinusoids and intrahepatic shunts are also major determinants effective hepatocyte perfusion, which is a major determinant of liver failure.

Fig 7: Natural history of chronic liver disease



MORPHOLOGY OF CIRRHOSIS

Grossly with the naked eye, a cirrhotic liver appears nodular, “hub nailed” on the external surface and nodular on cut section. Cirrhosis can be categorized based on its morphology, into micronodular or macronodular variety. The most common one Micronodular cirrhosis implies that almost all the regenerative nodules are small and less than 3mm in diameter (9). It mostly seen in patients with injury due to hepatotoxic agent or metabolic disorder uniformly affects the lobules (eg.alcohol). In alcoholic liver diseases the product acetaldehyde has many hepatotoxic effects like inducing steatosis, increased sensitization to TNF

alpha mediated hepatic necrosis, forming neoantigens by various mechanisms. Micronodules rarely contain portal tracts or terminal hepatic veins. Cirrhotic macronodules consists of residual portal structures and central veins, which are not bound by septa. Its diameter varies from 3mm to several centimeters. Macronodular cirrhosis is due to viral hepatitis and arises after continued massive collapse of cirrhotic parenchyma, promoting accentuated regeneration[10]. Microscopic changes include presence of nodule and fibrous septa with effacement of lobular architecture. The nodules are of two types.

i. Dissection type

ii. Hyperplastic regenerative nodules

Dissection nodules contains portal tracts and central veins separated by fibrous septa. In hypoplastic nodule no bile duct will be there which is known as "vanishing duct syndrome". Although regenerative nodules are benign, it is not uncommon that some progress and undergo dysplastic and malignant change and go through carcinogenic pathway to become malignant nodules or hepatocellular carcinoma[17].

EVOLUTION OF CIRRHOSIS

It can be assessed on degree of fibrosis and nodule formation. Following stages are seen in needle biopsy

- Incomplete septal- incomplete bridging fibrosis, no nodules
- Early- thin bridging fibrosis and dissecting nodules
- Moderately advanced-thick fibrosis
- Advanced-wide septa and regenerative nodular hyperplasia

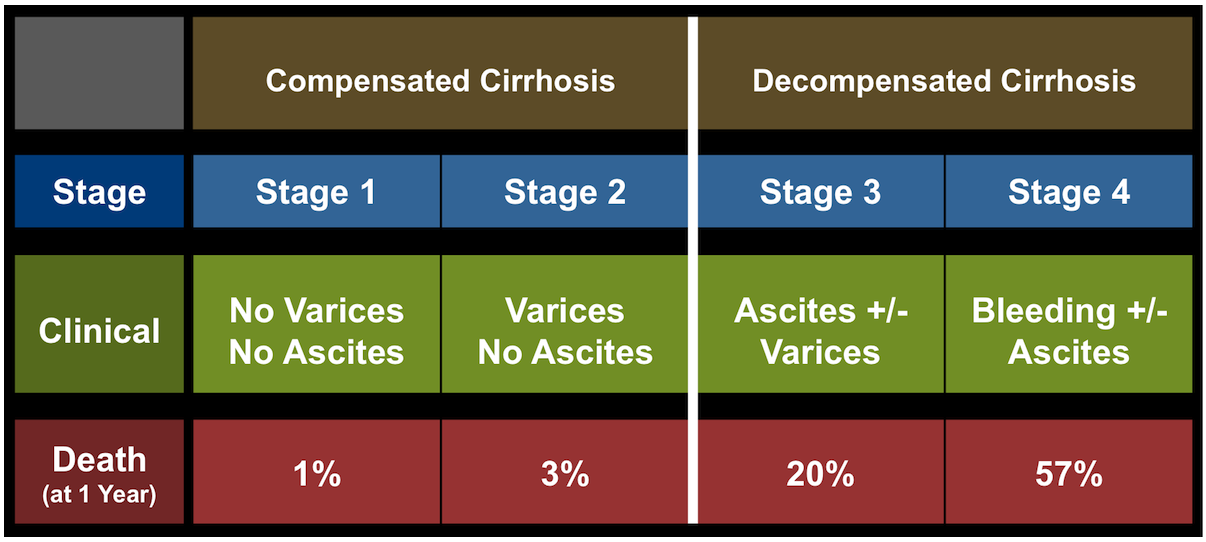
HEMODYNAMIC ALTERATIONS

Apart from complex molecular processes involved in fibrogenesis and the formation of regenerative nodules in cirrhosis, modifications of the angioarchitecture are also considered one of the important pathological views. These changes are necessary to convert compensated cirrhosis into decompensated stage. Changes are including Sinusoidal capillarization, neoangiogenesis and the formation of intrahepatic shunts, increase the intrahepatic vascular resistance leading to various complications.

SINUSOIDAL CAPILLARIZATION

Sinusoidal capillarization includes microcirculatory distortions in the liver. Sinusoidal endothelial cells play a key role in chronic liver disease initiation and progression , through four key processes which includes, sinusoidal capillarization, angiogenesis and vasoconstriction. Capillarization also called as dedifferentiation, occurs following liver injury. Capillarization is the preliminary step in the event of fibrogenesis. Liver sinusoidal endothelial cells (LSEC) are able to maintain hepatic stellate cells in quiescent stage as long as it is differentiated. So differentiated LSEC are ‘gatekeepers of fibrosis’. VEGF contributes mainly in maintenance of LSEC differentiation.

Fig. 8:Stages of cirrhosis.



The cirrhotic liver reduces the number and size of the fenestrae which acts as barrier. The fenestrated sinusoids are thus transformed into continuous and more rigid capillaries (sinusoidal capillarization), which contribute further to the increasing intrahepatic (sinusoidal hypertension) vascular resistance and the subsequent development of portal hypertension. The limited permeability of the sinusoids deprives the hepatocytes of nutrients and hampers the ability to perform vital metabolic functions. Sinusoidal capillarization hence major contributary factor to liver failure, regardless of the metabolic capacity of hepatocytes. [18,19 & 20]

ANGIOGENESIS AND INTRAHEPATIC SHUNTS

In cirrhosis the main vascular abnormalities are angiogenesis (development of new vessels from preexisting vessels) and the presence of intrahepatic shunts. Both vascular abnormalities predominate along the regions of active inflammation and fibrous septa. Hepatic angiogenesis occurs during

fibrogenesis and these two processes are closely interlinked with one another. Liver fibrosis enhances angiogenesis and, in turn liver angiogenesis aggravates liver fibrosis. The vascular endothelial growth factor (VEGF) will undergo transcription and up regulation occurs by hepatic stellate cells to stimulate angiogenesis. The sustained hypoxic state when ischemia ensues in fibrotic areas will lead to angineogenesis to compensate the blood supply and to restore the hepatic blood circulation [21,22].

The intrahepatic shunts thus impoverish the surviving parenchyma of nutritive blood supply, and thereby contribute to hepatocellular necrosis[10]. The fibrotic processes obliterate the low pressure portal vein system, while hepatic arteries are high pressure system, less likely to be obliterated. As a response, the HABR (hepatic artery buffer response) compensatory mechanism increases the part of hepatic blood flow derived from the hepatic artery[23]. Arteriovenous anastomoses are helpful in redistributing the elevated arterial pressure to the portal vein and, hence contribute to portal hypertension [10].

CIRRHOTIC ANGIOARCHITECTURE

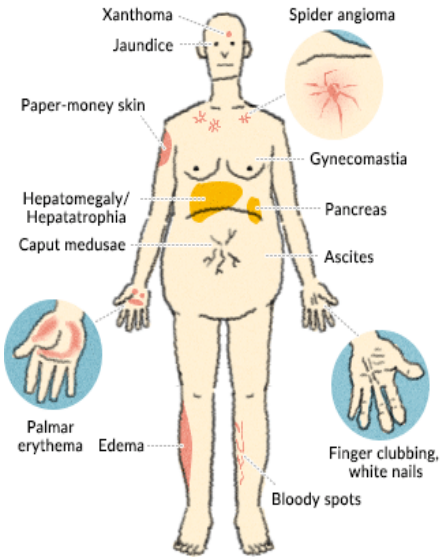
The normal lobular angioarchitecture almost completely disappears in a cirrhotic liver due to persistent damage to portal fields and sinusoids. While chronic hepatitis lacks the presence of regenerative nodules, spatial disarrangements of hepatocytes and alterations of the angioarchitecture already appear in this earlier stage of the process toward cirrhosis. Fibrous bridges, connecting an enlarged portal tract and hepatic vein, contain numerous tortuous

and intermingled blood vessels. Portal vein branches run in parallel, of which only a few extend outwards into the parenchyma to give nourishment to hepatocytes. Those rather small veins resemble point-like inflow sources and provide the nutrition for liver cells to regenerate. When regenerative nodules become cut off from portal blood supply, hepatic artery will take over to the maintenance of the nodules formation and progression[5]. Another hypothesis, suggest that angiogenic pathways are activated within regenerative nodules to promote the formation of new blood vessel[10].

CLINICAL FEATURES AND COMPLICATIONS

Based on clinical terms, cirrhosis can be described as are either compensated or decompensated. Decompensation implies the manifestation of clinically evident complications resulting from either portal hypertension or liver insufficiency (jaundice, ascites, hepatic encephalopathy or bleeding varices). Ascites is usually the first sign most of the times. Hepatorenal syndrome, hyponatremia and spontaneous bacterial peritonitis are features of decompensation when it is complicated by ascites. Compensated cirrhosis, on the other hand, is asymptomatic almost always, as the liver is able to compensate for the incurred liver damage. However, it can progress to decompensation during the course of the time [24].

Fig 9: Clinical features



Symptoms of liver cirrhosis

- General malaise, fatigue
- Anorexia / weight loss
- Feeling of enlarged abdomen
- Swollen abdomen / legs
- Nose bleed / bleeding from lower limbs
- Jaundice / itch
- Hand tremors

Physical findings

- Skin pigmentation
- Xanthoma
- Spider angioma
- Palmar erythema
- Finger clubbing (hepatopulmonary syndrome)
- Caput medusae
- Gynecomastia
- Fever
- Hepatoceleoma
- Hepatic halitosis (dimethyls -ulphide, ketons in the expired breath)
- Jaundice
- Ascites, lower thigh edema
- Hepatic encephalopathy
- Bleeding plaque / purpura

Akuko Wakuta etc., Hepatobiliary and pancreas, 73(6), 979-984, 2016 (Partially modified)

SIGNS OF HEPATOCELLULAR FAILURE

There are many clinical and pathological associations are implicated in cirrhosis.

GASTROINTESTINAL

Splenomegaly and abdominal wall venous collaterals are encountered in portal hypertension. Varices are seen in OGD scopy. Peptic ulcers has been found to be associated with 11% of patients. Small bowel bacterial overgrowth and microbial transformation accounts for 30%. Gall stones are of usually pigment type. Parotid enlargement and chronic pancreatitis are also seen.

Fig 10: Portal hypertensive gastropathy & oesophageal varices

RENAL

Hepatorenal syndrome is single most common association found. Cirrhotic glomerular sclerosis also has been found.

FOETOR HEPATICUS

This sweetish, slightly feculent odour of breath is due to dimethyl sulphide and ketones in alveolar air, which is helpful first sign in patients presenting in coma.

DERMATOLOGICAL

1. VASCULAR SPIDERS

Arterial spiders are found in the territory of superior vena cava and rarely below the line of nipples. It ranges in size from pinhead to 0.5cm in diameter. Vascular spider and clubbing seen in hepatopulmonary syndrome. Paper money skin seen in advanced cirrhosis.

2. PALMAR ERYTHEMA

The hands are warm and bright red in colour especially in hypothenar and thenar eminences and pulp of fingers. Mechanism of skin changes are due to estrogen excess found in liver cirrhosis. Mostly oestrodiol/ free testosterone ratio is highest in male cirrhotics.

Fig 11: Palmar erythema & spider naevi

3. LEUCONYCHIA

These are related to hypoalbuminemia and malnutrition.

4. DUPUYTREN'S CONTRACTURE

This is thickening of the palmar fascia in the hands. This may be idiopathic.

Fig 12: Dupuytren's Contracture

NUTRITION

Severe malnutrition and steatorrhea are found in cirrhotic patients. Increased resting energy expenditure (REE) may be the factor responsible for this malnutrition.

ENDOCRINE

- **HYPERGLYCEMIA**

80% of the cirrhotic patients are glucose intolerant and only 20% of them are diabetic.

- **HYPOGONADISM**

Diminished libido and potency are frequently seen in males. Loss of secondary sexual characters in males like testicular failure and in females premenopausal ovarian failure are common. Loss of feminine characters in females like pelvic pad of fat and breast tissue loss. Gynaecomastia is due to enlargement of glandular tissues.

EYE SIGNS

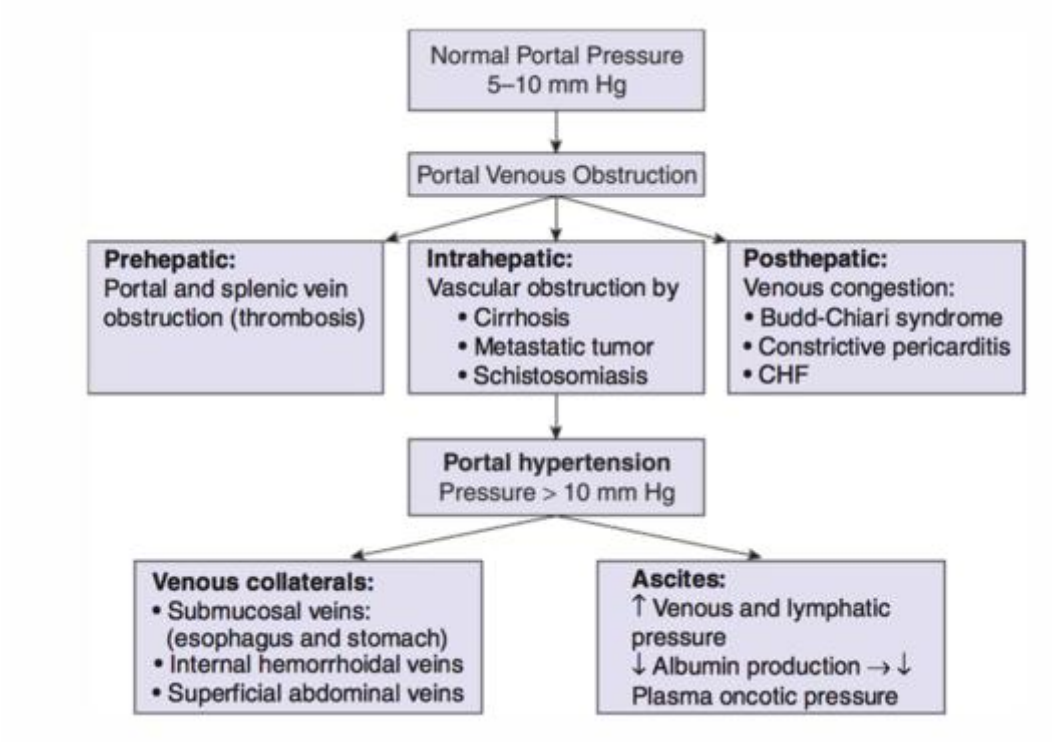
Lid retraction and lid lag are significantly found increased in patients.

PORTAL HYPERTENSION

Portal hypertension is the major complication of all type of cirrhosis and the primary event is obstruction or increased resistance in the portal blood flow. Portal venous blood bypasses the liver cells and diverted into collaterals hence

bypassing the detoxifying functions and is shunted directly into the hepatic venous radicles in the fibrous septa.

Fig.13. Formation of Portal Hypertension



These portohepatic anastomoses develop from pre - existing sinusoids enclosed in the septa. Even larger porto-hepatic venous anastomoses are found in the cirrhotic liver. About one third of the total blood flow perfusing the cirrhotic liver may bypass sinusoids, and so that it bypass the functioning liver tissue, through these channels. The obstruction to portal flow is due to nodules which compress hepatic venous radicles which leads to a postsinusoidal portal vein obstruction hence portal hypertension. However, in cirrhosis with sinusoidal portal hypertension, the difference between wedged hepatic venous (sinusoidal) pressure (WHVP) and free hepatic venous pressure (FHVP) that is hepatic venous pressure gradient (HVPG) i.e main portal pressures are virtually identical

and the stasis must extend to the portal inflow vessels. The normal HVPG is 5-6mmHg and when it exceeds 10mmHg represents clinically significant portal hypertension and complications may ensue at any time with that pressure. Sinusoids probably provide the greatest resistance to flow. Changes in the space of Disse, especially collagenization, result in sinusoidal narrowing and this is important in the alcoholic. Portal hypertension may ensue in cirrhotic livers as a consequence of regenerative nodules and fibrous tissue cuddled with hyperdynamic circulation. Portal pressure measurement can be performed at the time of transjugular liver biopsy.

ASCITES

Ascites is the accumulation of excessive free fluid within the peritoneal cavity. It is most commonly encountered first sign of decompensation in patients with cirrhosis. Incidence is 48% of patients. There are number of other disorders lead to either transudative or exudative ascites.

PATHOGENESIS

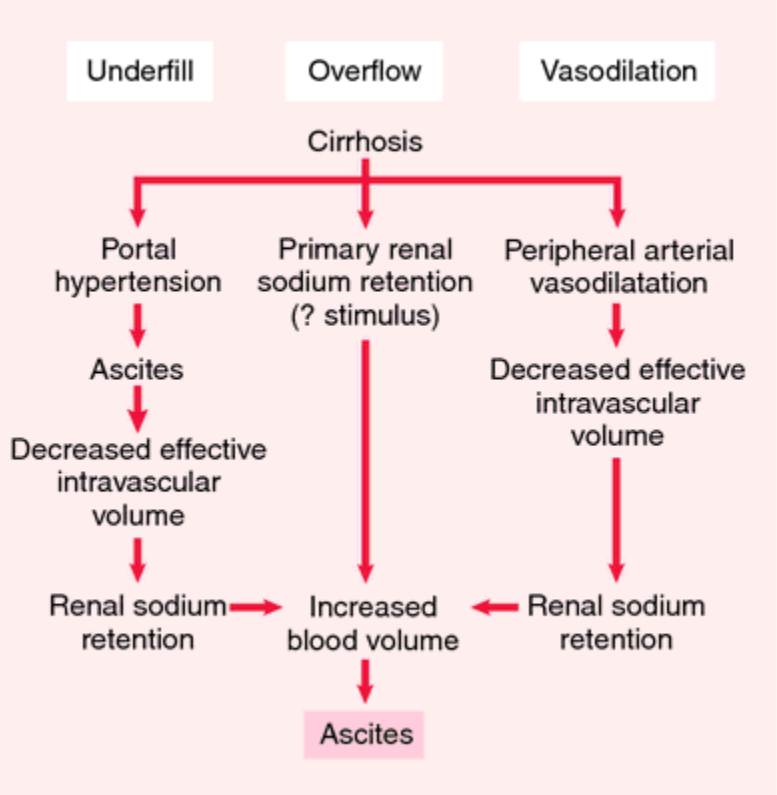
The accumulation of ascitic fluid represents a state of sodium and water retention, but the event is complex mechanism. Renal system is playing the main role Two widely accepted theories have been proposed.

First one the “Underfilling” theory or peripheral vasodilation theory suggests that the primary event is inappropriate sequestration of fluid within the splanchnic vascular bed due to sinusoidal portal hypertension and a consequent decrease in effective circulating blood volume. According to this theory, an

apparent decrease in intravascular volume (underfilling) because of peripheral vasodilation, is sensed by the kidney, which responds by retaining salt and water secondary to renin-angiotensin-aldosterone axis activation.

Second one the “Overflow” theory suggests that the primary abnormality is inappropriate renal retention of salt and secondary to hepatic insufficiency or sinusoidal hypertension in the absence of volume depletion. Increased sympathetic output results in diminished natriuresis by activation of the renin-angiotensin system and diminished sensitivity i.e renal resistance to atrial natriuretic peptide. Portal hypertension plays an important role in the formation of ascites by increasing hydrostatic pressure within the splanchnic capillary bed that leads to extravasation of fluid into the third space i.e peritoneal cavity. Hypoalbuminemia which leading to reduced plasma oncotic pressure also favor the extravasation of fluid. Hence ascites is infrequent in patients with cirrhosis unless either or both portal hypertension and hypoalbuminemia are present. Hepatic lymph may seep freely from the surface of the cirrhotic liver due to distortion and obstruction of hepatic sinusoids and lymphatics and contribute to ascites formation.

Fig 14: Theories of ascites



VARICES (COLLATERAL CIRCULATION)

Extensive portal – systemic venous communications develop in order to decompress or bypass the high – pressure portal venous system. Maintenance of portal pressure after the collateral are formed, is attributed to a increase in splanchnic blood flow and splanchnic vasodilation. Splanchnic vasodilation is main factor in maintaining hyperdynamic circulation in cirrhosis

MAJOR SITES OF COLLATERALS

- Oesophageal and gastric fundal varices (Left gastric vein, posterior gastric and short gastric vein join of portal system with intercostal, diaphragmo-oesophageal and azygos veins of the caval system).

- Heamorrhoids (Superior haemorrhoidal vein of the portal system with middle and inferior haemorrhoidal veins of the caval system).

- Caput medusa (Remnants of the umbilical circulation of the foetus present in the falciform ligament through a large paraumbilical vein).

- Other sites of anastomoses are retroperitoneal vein, lumber vein and veins over bare area of the liver.

VARICEAL BLEEDING

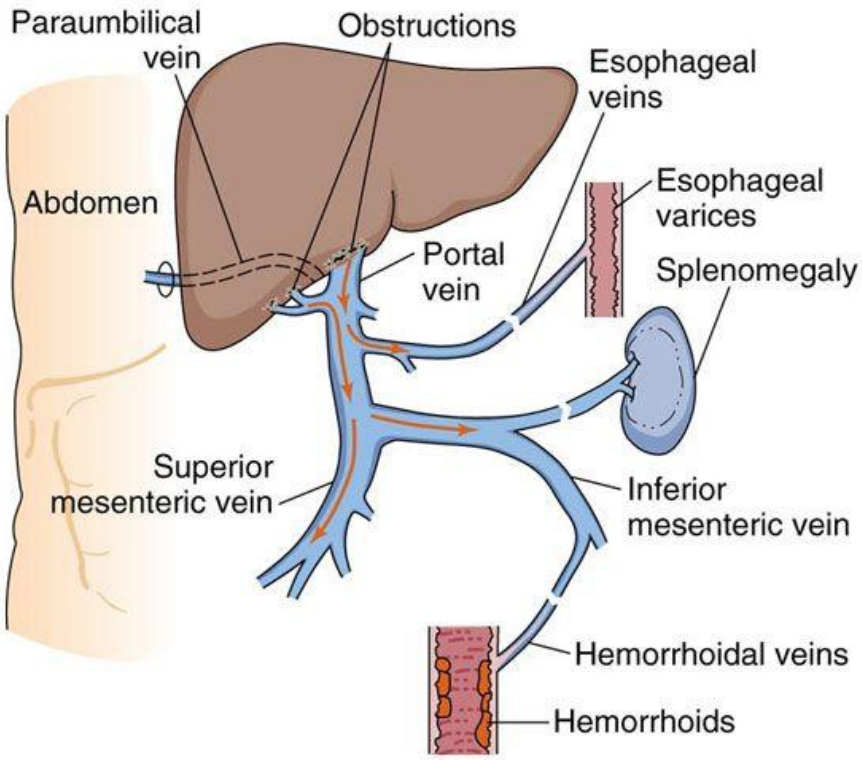
Variceal bleeding occurs when portal venous pressure is more than 12 mmHg in contrast varices are formed even when the portal venous pressure is 10mmHg. Mostly bleeding arises from oesophageal varices within 3 to 5 cm of the oesophago-gastric junction or from gastric fundal varices.

FACTORS PREDISPOSING TO BLEEDING

- Large varices(>5mm diameter)
- Endoscopic variceal stigma (cheery red spots and red wheal markings representing large varix)
- High portal pressure (12mmHg)
- Liver failure
- Drugs (NSAIDs)
- portal hypertensive gastropathy / coagulopathy

The presence of varices can be predicted by using platelet/ spleen diameter ratio with positive predictive value of 2.77 and negative likelihood ratio of 0.13.

Fig. 15. Varices

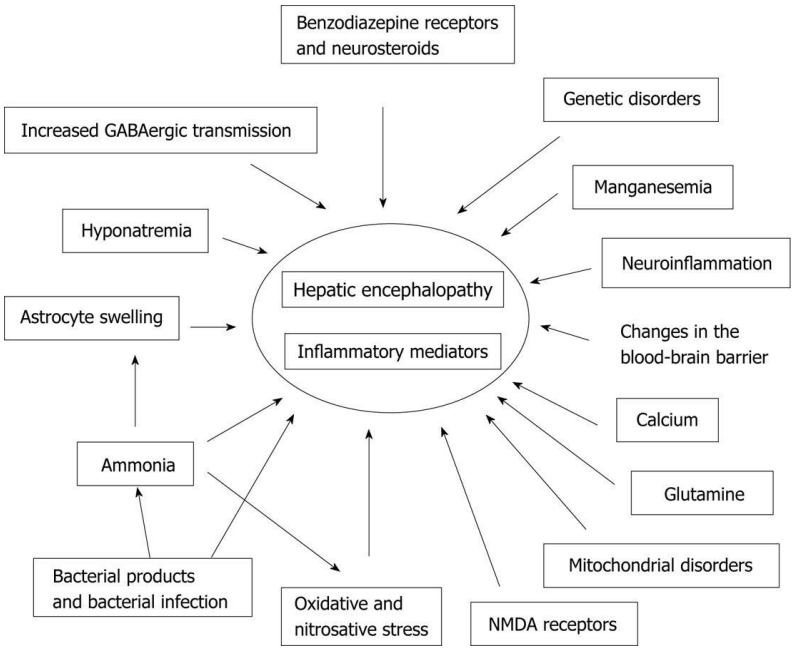


HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy is the term used to describe the complex and variable changes in neuropsychiatric status that complicate liver disease. In patients with cirrhosis, a spectrum of neuropsychiatric abnormalities exists, ranging from clinically indistinguishable changes in cognition to clinically obvious changes in the intellect, behavior, motor function and consciousness. Both hepatic failure and portal systemic shunts are key elements of hepatic encephalopathy. Principally gut derived neurotoxin, ammonia, escape the hepatic

metabolism and reaches the brain. This ammonia is detoxified by astrocytes in brain. This process results in lo grade cerebral edema, which eventually impacts the neural function. The hyperdynamic circulation is probably caused by an overproduction of nitric oxide. Hepatic encephalopathy clinically classified into overt and covert encephalopathy. Overt encephalopathy further claasified into episodic and persistent variety.

Fig.16. Factors predisposing to Hepatic Encephalopathy



In addition, portal hypertension results in the development of portosystemic collaterals. These alternative channels bypass the liver and guide a part of the increased portal blood flow directly into the systemic venous system without detoxification. Both hepatocellular failure and portosystemic shunting of blood play an equal role in hepatic encephalopathy[26]

Fig.17. Management of Hepatic Encephalopathy

Table. Current and Future Agents for Hepatic Encephalopathy

Agent	Clinical Trials	Dosing	Use
Lactulose	Elkington et al,[2] 1969	10-20 g PO/PR, titrate to 2-3 stools	FDA approved: acute and chronic encephalopathy
Rifaximin	Lawrence and Klee,[6] 2008	550 mg PO BID	FDA approved: chronic encephalopathy
Sodium benzoate + sodium phenylacetate	Mendenhall et al,[7] 1986	5.5 g/m^2 IV over 90-120 min, repeat daily	FDA approved: acute encephalopathy
Glycerol phenylbutyrate	Rockey et al,[8] 2014	5-12.4 g/m^2 daily	Phase 2 trial
Ornithine phenylacetate	Vetura-Cots et al,[9] 2013	10 g IV daily	Phase 2 trial: acute encephalopathy

SPONTANEOUS BACTERIAL PERITONITIS

The most common infection in cirrhosis is spontaneous bacterial peritonitis (SBP). It is defined as infection of ascitic fluid in the absence of recognizable secondary cause of peritonitis. It is predominantly associated with an ascitic protein of <1gm/dL, in which case the defective opsonization of microorganism in ascitic fluid occurs. Spontaneous Bacterial Peritonitis (SBP) contributes 30% of all infections in cirrhosis and 9% of hospitalized population. SBP is blood borne and mostly monomicrobial. Microbial translocation is the key factor responsible for SBP.

ORGANISMS

Coliforms, Streptococci, Camphylobacter; usually infection is blood – borne. Ascitic fluid infection can also be due to *staph. Aureus* and group D streptococci, E*nterococcus*. *E. coli* infection is more common. Anaerobic bacteria are rarely found. Half patients show blood culture positivity.

MECHANISM

Bacterial translocation from the gut through mesenteric node. Culture are more likely to be positive when 10 ml of ascetic fluid is inoculated into two culture bottles when the ascitic fluid protein <1gm/dl. If more than two organisms are identified in culture, secondary bacterial peritonitis due to surgical causes should be considered.

HEPATORENAL SYNDROME

The haemodynamic alteration in kidneys are due to decreased effective blood volume and increased sympathetic tone. Hepatorenal syndrome is the development of renal failure in patients with severe liver disease in the absence of renal parenchymal pathology. It represents the vascular and neurohumoral changes that occur during ascites formation. The five- year probable survival rate is 11%. Involvement of endothelin – 1and 3 has been implicated in hepatorenal syndrome. Role of nitric oxide has also been suggested as one of the mechanisms.

Following six criteria must be fulfilled to encounter the diagnosis of HRS:

- Cirrhosis with ascites
- Serum creatinine > 1.5 mg % (>133umol/L)
- Absence of other causes of renal failure as evidenced by proteinuria > 500 mg/dl, urine RBC> 50/HPF and abnormal renal USG.
- No evidence of treatment with nephrotoxic drugs/vasodilators.

- Absence of shock
- Absence of sustained improvement of renal function following at least 2 days of diuretic withdrawal and volume expansion with albumin (decrease in serum creatinine to 1.5mg/dl or less)

TYPES OF HRS

a) Type 1- rapidly progressive type over less than 2 weeks
b) Type 2- slowly progressive type

HEPATOPULMONARY SYNDROME

About one third of patients with decompensated cirrhosis have been suffered from hepatopulmonary syndrome in the form of reduced arterial saturation and cyanosed. This is defined as a clinical disorder associated with advanced liver disease, arterial hypoxemia, pulmonary vascular dilation in the absence of primary cardiopulmonary disease.

Components of Hepatopulmonary syndrome (HPS)

- Advanced Chronic Liver Disease
- Arterial Hypoxemia (Decreased Pao2)
- Intra – Pulmonary Vasodilatation
- No Primary Cardio – Pulmonary Disorder[26].

Laboratory Evaluation

No serologic test can diagnose cirrhosis accurately.[3] The term liver function tests is a misnomer because the assays in most standard liver panels do not reflect the function of the liver correctly.[10] When a liver abnormality is suspected, a liver panel, a complete blood count (CBC) with platelets and prothrombin time test should be performed.[14] Common tests in standard liver panels include the serum enzymes aspartate transaminase (AST), alanine trans-aminase (ALT), alkaline phosphatase and g-glutamyl-transferase; total, direct, and indirect serum bilirubin; and serum total protein and albumin. The ALT is thought to be the most cost-effective screening test for identifying metabolic or drug-induced hepatic injury. One study found that a platelet count of less than 160 K per mm^3 has a sensitivity of 80 percent for detecting cirrhosis in patients with chronic hepatitis C.[16]

A prospective study showed a strong correlation between liver function test results elevated to greater than twice the upper limit of normal for at least six months and underlying liver disease proved by liver biopsy.[17] Additional serologic studies should be pursued in such circumstances to evaluate for various etiologies of cirrhosis. If clinical suspicion for liver disease is high, then further serologic work-up is warranted within six months.[15] If a patient has a persistently increased ALT level, viral hepatitis serologies should be assayed. If these are negative, the remaining serologic work-up should include an antinuclear antibodies test or anti–smooth muscle antibody test, or both, to evaluate for autoimmune hepatitis; and a fasting transferrin saturation level or iron-binding

capacity and ferritin level[18] to evaluate for hereditary hemochromatosis.[15] In patients younger than 40 years in whom Wilson's disease is suspected, serum ceruloplasmin and serum and urinary copper levels should be measured. Primary biliary cirrhosis or primary sclerosing cholangitis should be suspected in patients with chronic cholestasis. Testing for a_1-antitrypsin (A_1AT) deficiency may be of benefit in patients with chronic hepatic injury and no other apparent cause. Ultrasonography or biopsy is necessary to establish the diagnosis of NAFLD.

Radiographic Studies

Although various radiographic studies may suggest the presence of cirrhosis, no test is considered a diagnostic standard.[3] The major use of radiographic studies is to detect ascites, hepatosplenomegaly, hepatic or portal vein thromboses, and hepatocellular carcinoma, all of which strongly suggest the diagnosis of cirrhosis.

Ultrasonography

Abdominal ultrasonography with Doppler is a non-invasive, widely available modality that provides valuable information regarding the gross appearance of the liver and blood flow in the portal and hepatic veins in patients suspected to have cirrhosis. Nodularity, irregularity, increased echogenicity and atrophy are ultrasonographic hallmarks of cirrhosis. In advanced disease, the gross liver appears small and multinodular, ascites may be detected, and Doppler flow can be significantly decreased in the portal circulation. The discovery of

hepatic nodules in ultrasonography warrants further evaluation because benign and malignant nodules can have similar ultrasonographic appearances.

C T AND MRI

CT and magnetic resonance imaging (MRI) generally are poor at detecting morphologic changes associated with early cirrhosis, but they can accurately demonstrate nodularity and lobar atrophic and hypertrophic changes, as well as ascites and varices in advanced disease. Although MRI sometimes differentiates among regener-ating or dysplastic nodules and hepatocellular carcinoma, it is best used as a follow-up study to determine whether lesions have changed in appearance and size.[20] CT portal phase imaging can be used to assess portal vein patency, although flow volume and direction cannot be deter-mined accurately.[22]

Although used rarely, magnetic resonance angiography (MRA) can assess portal hypertensive changes including flow volume and direction, as well as portal vein thrombosis.[22] One study reported that MRI can accurately diagnose cirrhosis and provide correlation with its severity.[23]

Liver Biopsy

Liver biopsy is performed via percutaneous, transjugular, laparoscopic, open operative, or ultrasonography or CT-guided fine-needle approaches. Before the procedure, a CBC with platelets and prothrombin time measurement should be obtained. Patients should be advised to refrain from consumption of aspirin

and nonsteroidal anti-inflammatory drugs for seven to 10 days before the biopsy to minimize the risk of bleeding.

Transient elastography (fibroscan)

It is a non-invasive method of evaluating liver fibrosis / cirrhosis.

LIPID METABOLISMS

LIPID CHEMISTRY

Lipid constitutes a heterogenous group of components of biochemical importance. Its defined as compounds which are relatively insoluble in water but soluble in nonpolar organic solvents like benzene, chloroform, ether, alcohol and acetone. Although occasionally the terms lipids and lipoids are used synonymously. Lipids are waxy, greasy, oily compounds of the body. In our human body fat serves as an efficient source of energy, except for the brain. Caloric value of fat is 9kcl/gm. Combination of lipids and protein (lipoprotein) are important cellular cytoplasmic and cell wall constituents. They form important dietary constituents as an account of their high calorific value and the fat-soluble vitamins and the essential fatty acids contained in them[28,29].

CHEMICAL CLASSIFICATION OF LIPIDS

- **Simple lipids**

They are esters of fatty acids with glycerol or other alcohol

- **Compound lipids**

They are fatty acids esterified with alcohol with additional group (phospholipids and non-phosphorylated lipids)

- **Derived lipids**

They are derived from lipids and precursors of lipids (steroids, fatty acids)

- **Complex lipids**

FUNCTIONS OF LIPIDS

In general lipids are important as;

- ✓ Structure of cell membranes (phospholipids and cholesterol)
- ✓ As ready source of energy, because lipids supply over half of the energy utilized in basal metabolism (trigycerides)
- ✓ Metabolic regulators (steroid hormones and prostaglandins)
- ✓ Act as surfactants, detergents and emulsifying agents (amphipathic lipids)
- ✓ Gives shape and contour of the body
- ✓ Protect internal organs by providing cushioning effect
- ✓ Helps in absorption of fat soluble vitamins
- ✓ Structure of sex hormones.
- ✓ Thermal blanket, because their presence in subcutaneous tissue insulates the body against heat loss.

FATTY ACIDS

They are included in the group of derived lipids. They are carboxylic acids obtained from the hydrolysis of mainly glycerol and cholesterol. They classified based on odd or even number of carbon atoms and depending on the length of hydrocarbon chain and nature of hydrocarbon chain whether it is saturated or unsaturated or branched chain or hydroxy fatty acids. The chain may be saturated (containing no double bonds) or unsaturated (containing one-mono-unsaturated or more- poly unsaturated double bonds). The main saturated fatty acids are palmitic and stearic acid.

Unsaturated fatty acids are again subdivided into:

- Monounsaturated (mono-enoic acids).
- Poly unsaturated (Poly-enoic acids).

Fatty acids are aliphatic carboxylic acids, and have given general formula of R-CO-OH. In which carboxylic acid group represents the functional group. Normal Values: 250-400 mg/dl. Free fatty acids are readily available source of energy and fulfills majority of the energy requirements in our body[28, 29].

CHOLESTEROL

It was first described during the end of 18th century by French chemist De Fourerol. It is distributed in almost all cells of the body as a component of cell membrane particularly in nervous tissue. Cholesterol is the most important compound of those classed as sterols. It is a precursor of bile acids, the steroid hormones and Vitamin D. Out of total 27 carbon atoms its having one hydroxyl

group at the position of 3rd atom. Esterification occurs at this position by lecithine cholesterol acyl transferase. With fatty acids, it forms waxes. It is a stable white crystalline substance insoluble in water but readily soluble in solvents like chloroform, ether, alcohol, and other fat solvents. The cholesterol is present in high amounts in nervous tissue (2%), liver (0.3%), skin (0.3%) and intestine (0.2%) and certain endocrine glands [27&29].

The relative high content of the cholesterol in skin may be related to vitamin D formation and that in adrenals to steroid hormones synthesis and gonads. Much attention being directed towards cholesterol at present era, not only because of it is related to other steroids in the body, but also because cholesterol is involved in degenerative changes in the arterial wall known as atherosclerosis, major reason for cardiovascular mortality.

Normal Values: Range from 160-240 mg/dl.

TRIGLYCERIDES (TRIACYLGLYCEROLS)

The liver and adipose tissue are the major sites of triacylglycerol synthesis. Triacylglycerols, so called neutral fats, are esters of the alcohol glycerol and fatty acids. The TAG synthesis in adipose tissue is for storage of energy while in liver it is mainly secreted as VLDL and is transported. On hydrolysis triglycerides yield 3 fatty acid, and 1 molecule of glycerol when it is boiled together with an alkali saponification occurs[27 &29]. It contributes major component of chylomicron.

Normal values: 40-150 mg%.

PHOSPHOLIPIDS

Phospholipids are complex lipids, resembling triglycerides, but along with glycerol and fatty acids it also contains phosphate and a nitrogenous base. The major phospholipids in plasma are lecithin which is amphipathic lipid and sphingomyelin, the only phospholipid that contain phosphate and have no sugar moiety. The phosphoric acid and nitrogenous base choline are forming polar head which is water-soluble. Lipids since they are insoluble in water, are carried in the plasma in the form of lipoprotein complexes. These complexes of lipid and protein impart solubility, and all lipids enter and travel through the blood stream as lipid-protein complexes. The protein part of it is known as apolipoprotein.

STRUCTURE OF A LIPOPROTEIN PARTICLE

The lipoprotein particle contains a hydrophobic core of triglyceride and cholesterol ester, surrounded by a coat containing polar phospholipids, free cholesterol. Lipoproteins are classified by their buoyant density, which inversely reflects their size. The greater the lipid to protein ratio, the larger their size and the lower the density. Lipoproteins can be classified into five main groups. The first three are triglyceride rich and, because of their large size, they scatter light, which can give plasma a turbid appearance (lipaemic) if present in high concentrations:

TABLE : Characteristics of major lipoproteins

Lipoprotein	Source	Composition (% mass)				Apolipoprotein	Electrophoretic mobility
		Pro	Cho	TGL	PL		
Chylomicrons	Gut	1	4	90	5	A, B, C, E	Origin
VLDL	Liver	8	25	55	12	B, C, E	Pre-*b*
LDL	VLDL via IDL	20	55	5	20	B	*B*
HDL	Gut/liver	50	20	5	25	A, C, E	*A*

Cho, cholesterol; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; PL, phospholipid; Pro, protein; TGL, triglyceride; VLDL, very low-density lipoprotein.

- Chylomicrons are the largest and least dense lipoproteins and transport exogenous lipid from the intestine to all cells.
- Very low-density lipoproteins (VLDLs) transport endogenous lipid from the liver to cells.
- Intermediate-density lipoproteins (IDLs), which are transient and formed during the conversion of VLDL to low-density lipoprotein (LDL), are not normally present in plasma.

The other two lipoprotein classes contain mainly cholesterol and are smaller in size:

- Low-density lipoproteins are formed from VLDLs and carry cholesterol to cells.
- High-density lipoproteins (HDLs) are the most dense lipoproteins and are involved in the transport of cholesterol from cells back to the liver (reverse cholesterol transport). These lipoproteins can be further divided by density into HDL_2 and HDL_3.

If a lipaemic plasma sample, for example after a meal, is left overnight at 4°C, the larger and less dense chylomicrons form a creamy layer on the surface. The smaller and denser VLDL and IDL particles do not rise, and the sample may appear diffusely turbid. The LDL and HDL particles do not contribute to this turbidity because they are small and do not scatter light. Fasting plasma from normal individuals contains only VLDL, LDL and HDL particles.

In some cases of hyperlipidemia, the lipoprotein patterns have been classified (Fredrickson's classification) according to their electrophoretic mobility. Four principal bands are formed, based on their relative positions, by protein electrophoresis, namely *a* (HDL), pre-*b* (VLDL), *b* (LDL) and chylomicrons.

Intermediate-density lipoproteins in excess may produce a broad *b*-band. Some individuals with hyperlipidaemia may show varying electrophoretic patterns at different times. Ultracentrifugation (separation based upon particle buoyant density) or electrophoretic techniques are rarely used in routine clinical practice. Instead, the lipoprotein composition of plasma may be inferred from standard clinical laboratory lipid assays. As fasting plasma does not normally contain chylomicrons, the triglyceride content reflects VLDL. Furthermore, generally about 70 per cent of plasma cholesterol is incorporated as LDL and 20 % as HDL. The HDL particles because of their high density, can be quantified by precipitation techniques that can assay their cholesterol content by subtraction, although direct HDL assays are now used.

The **Friedewald equation** enables plasma LDL cholesterol concentration to be calculated and is used in many clinical laboratories:

LDL cholesterol = Total cholesterol – {HDL cholesterol-TGL/5}

This equation makes certain assumptions, like when the patient is fasting and the plasma triglyceride concentration does not exceed 4.5 mmol/L (otherwise chylomicrons make the equation inaccurate).

MAJOR CLASSES OF APOLIPOPROTEINS

Table: The main apolipoproteins and their common functions

Apolipoprotein	Associated lipoprotein	Function
A_1	Chylomicrons and HDL	LCAT activator
A_2	Chylomicrons and HDL	LCAT activator
B_{48}	Chylomicrons and VLDL	Secretion of chylomicrons/VLDL
B_{100}	IDL, VLDL, LDL	LDL receptor binding
C_2	Chylomicrons, HDL, VLDL, IDL	Lipoprotein lipase activator
C_3	Chylomicrons, HDL, VLDL, IDL	Lipoprotein lipase inhibitor
E	Chylomicrons, HDL, VLDL, IDL	IDL and remnant particle receptor binding

HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

NORMAL LIPOPROTEIN METABOLISM

Chylomicrons are formed from dietary fats and cholesterol absorbed in the Intestine by the intestinal mucosal cells. They are secreted into the lacteals of lymphatics, pass through the thoracic duct and eventually enter the systemic

circulation. Main sites of metabolism are adipose tissue and skeletal muscle. As chylomicron enter capillaries, they come in contact with lipoprotein lipase, an enzyme located on the surface of endothelial cells particularly in capillaries of adipose tissue and muscle. Lipoprotein lipase needs insulin for maintenance of its activity. The interaction of chylomicrons and lipoprotein lipase results in hydrolysis of triglyceride into fatty acids and glycerol following activation of LPL by Apo C II of chylomicron.

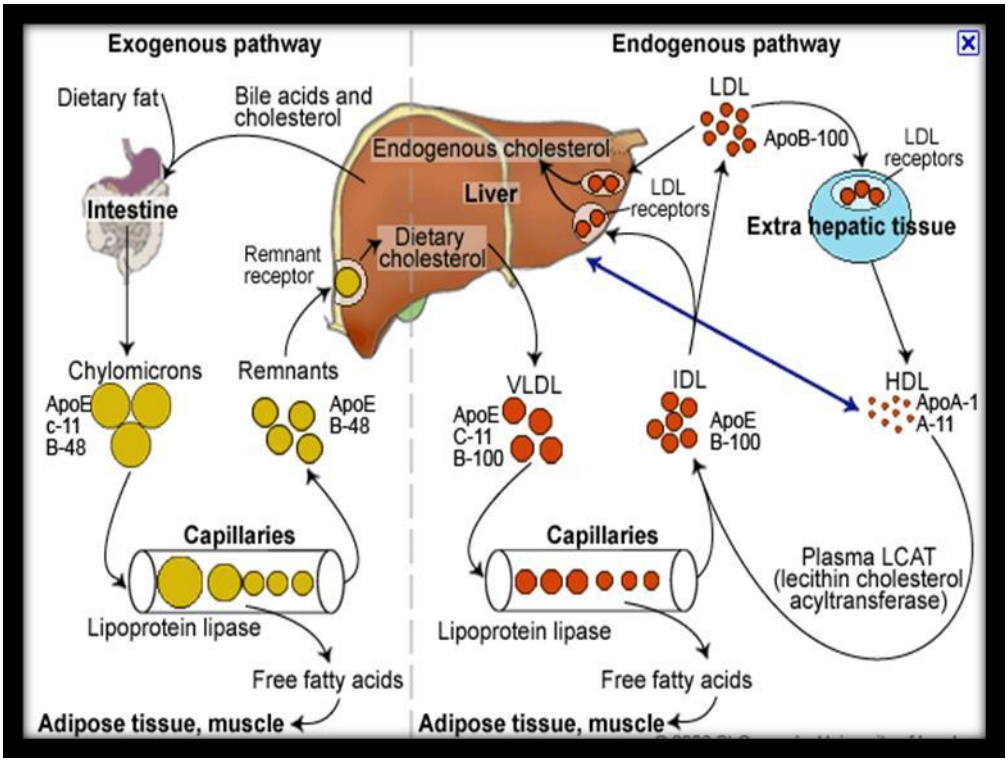
LIPID TRANSPORT

THE EXOGENOUS PATHWAY

The dietary triglycerides and cholesterol are incorporated into large lipoprotein complexes, so called chylomicrons within the intestinal epithelial cells. Cholesterol and fatty acids released from dietary fats by digestion together with bile are absorbed into intestinal mucosa cells where they are re-esterified to form cholesterol esters and triglycerides. These together with phospholipids and apoA and apoB are then secreted into the lymphatic system as chylomicrons. This secretion is dependent upon $apoB_{48}$. The chylomicrons enter the systemic circulation via the thoracic duct. Apolipoprotein C and apoE, both derived from HDL, are added to the chylomicrons in the lymph and plasma. The enzyme lipoprotein lipase is located on capillary walls and is activated by $apoC_2$ and inhibited by $apoC_3$. It hydrolyses triglyceride into fatty acids and glycerol. The former is taken up by adipose tissue or muscle cells or bound to albumin in the plasma. The glycerol component enters the hepatic glycolytic pathway. During

their travel within the circulation, the chylomicron particles get smaller and release some apoA and apoC along with phospholipids, which later become incorporated into HDL particles. The chylomicron remnants enriched in apoB and apoE and cholesterol then bind rapidly to hepatic LDL-receptor related protein, which recognizes the apoE ligand. Within the hepatic cells the cholesterol is utilised and the apolipoproteins catabolized. Thus, ultimately the exogenous pathway delivers triglyceride to adipose tissue and muscle and cholesterol to the liver.

Fig. 18: Lipid transport



THE ENDOGENOUS PATHWAY

Liver is the main source of endogenous lipids. Carbohydrates gets converted to fatty acids in the liver, it also esterifies the fatty acids with glycerol

to form triglycerides and most endogenous cholesterols getting produced in the liver. Hepatic cholesterols can either be derived from chylomicron remnant or from exogenous pathway or synthesized locally. From the liver lipids are transported as VLDL particles are transported to tissue capillaries. In peripheral tissues they are removed in the same way as chylomicrons (Hydrolysis by the Enzyme Lipoprotein Lipase).

Very low-density lipoprotein is a large triglyceride- rich particle consisting also of apoB_{100}, apoC and apoE. Following hepatic secretion of VLDL, it incorporates additional apoC from HDL particles within the circulation. Like chylomicrons, VLDL is hydrolysed by lipoprotein lipase in the peripheral tissues. The resulting VLDL remnant or intermediate density lipoprotein (IDL) contains cholesterol and triglyceride as well as apoB and apoE and is rapidly taken up by the liver or converted by the action of hepatic lipase to LDL by losing apoE and triglyceride.

Low-density lipoprotein is a small cholesterol-rich lipoprotein containing only apoB. It constitutes about 70 % of the total plasma cholesterol concentration. It can be taken up by most cells, although mainly the liver by the LDL receptor which recognizes and binds apoB_{100}. Within the cell, the LDL particles are broken down by lysosomes, releasing cholesterol. This cholesterol can be incorporated into cell membranes or in specific tissues such as the adrenal cortex or gonads and utilized in steroid synthesis.

Most cells are able to synthesize cholesterol, but, to avoid intracellular accumulation, there is a feedback control system reducing the rate of synthesis of the LDL receptors. Although most of the plasma LDL is removed by LDL receptors, if the plasma cholesterol concentration is excessive, LDL particles, by virtue of their small size, can infiltrate tissues by passive diffusion and can even cause damage, as in atheroma formation within arterial walls. An alternative route of removal of LDL is via the reticuloendothelial system, collectively termed the scavenger cell pathway, which recognizes only oxidized LDL.

The liver has a central role in cholesterol metabolism:

- Because liver contains most of the LDL receptors,
- It is responsible for most of the endogenous cholesterol synthesis,
- it takes up cholesterol from the diet via lipoproteins,
- it can excrete cholesterol from the body in bile.

Cholesterol is synthesized via a series of enzymatic steps, with HMG-CoA reductase being the rate-limiting enzyme. Suppression of this enzyme may occur if cholesterol synthesis is excessive. Involved in these processes is a family of transcription-regulating proteins called sterol regulatory element-binding proteins. Intracellular cholesterol accumulation also reduces the number of hepatic LDL receptors, and therefore LDL entry into cells declines and the plasma concentration rises. However, if the dietary intake of cholesterol is excessive, intracellular accumulation can occur. About 30–60 per cent of the dietary intake of cholesterol (of 1–2 mmol) is absorbed, this amount being

increased if the diet is rich in saturated fat. High saturated fat intake can also suppress LDL receptor activity and is a driver of cholesterol metabolism than dietary cholesterol. The richest dietary sources of cholesterol are egg yolks, dairy products and red meat.

Familial hyperlipidemias:

Table: Fredrickson's classification of hyperlipidaemias

Type	Electrophoretic	Increased lipoprotein
I	Increased chylomicrons	Chylomicrons
IIa	Increased *b*-lipoproteins	LDL
IIb	Increased *b* and pre-*b*-lipoproteins	LDL and VLDL
III	Broad *b*-lipoproteins	IDL
IV	Increased pre-*b*-lipoproteins	VLDL
V	Increased chylomicrons and pre-*b*- lipoproteins	Chylomicrons and VLDL

IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

IV. MATERIALS AND METHODS

SOURCE OF THE STUDY

Primary data collected by me from the cases of cirrhosis of liver from all causes getting admitted in medical wards of Coimbatore medical college hospital.

STUDY DESIGN

Cross-sectional study

STUDY PERIOD

July 2017 to June 2018.

METHODOLOGY

This is cross sectional study on lipid profile as an indicator of severity in cirrhosis of liver in 120 patients admitted to the medical ward in Coimbatore medical college of hospital with cirrhosis of liver due to various causes diagnosed clinically, biochemically and radiologically. Fasting serum lipid profile is measured in all patients diagnosed with cirrhosis. Total serum cholesterol, triglycerides and HDL were measured by direct method and serum LDL, VLDL has been calculated by using Friedewald formula.

LDL cholesterol = Total cholesterol – {HDL cholesterol-TGL/5}

VLDL = Sr. Triglycerides / 5

INCLUSION CRITERIA

- Patients age more than 18 years with cirrhosis

EXCLUSION CRITERIA

- Diabetes mellitus / hypertension
- Cerebrovascular disease
- Patients on lipid lowering drugs
- Pancreatitis
- Chronic kidney disease
- Hypo/hyperthyroidism

The primary collected by me was analyzed using SPSS 16.0 version software. Multiple variables between variable groups of single population done by using chi square test. Quantitative data between two or more groups were analyzed using ANOVA test.

V. RESULTS

TABLE 1: AGE DISTRIBUTION

AGE IN YEARS	NO OF PATIENTS	PERCENTAGE
20-29	6	5
30-39	19	15.8
40-49	43	35.8
50-59	40	33.3

In this study, mean age of the participants were 47.3 with the standard deviation of 9.1 which ranges from 20-65 years. Most participants are happened to be in the range of 40-60 years of age.

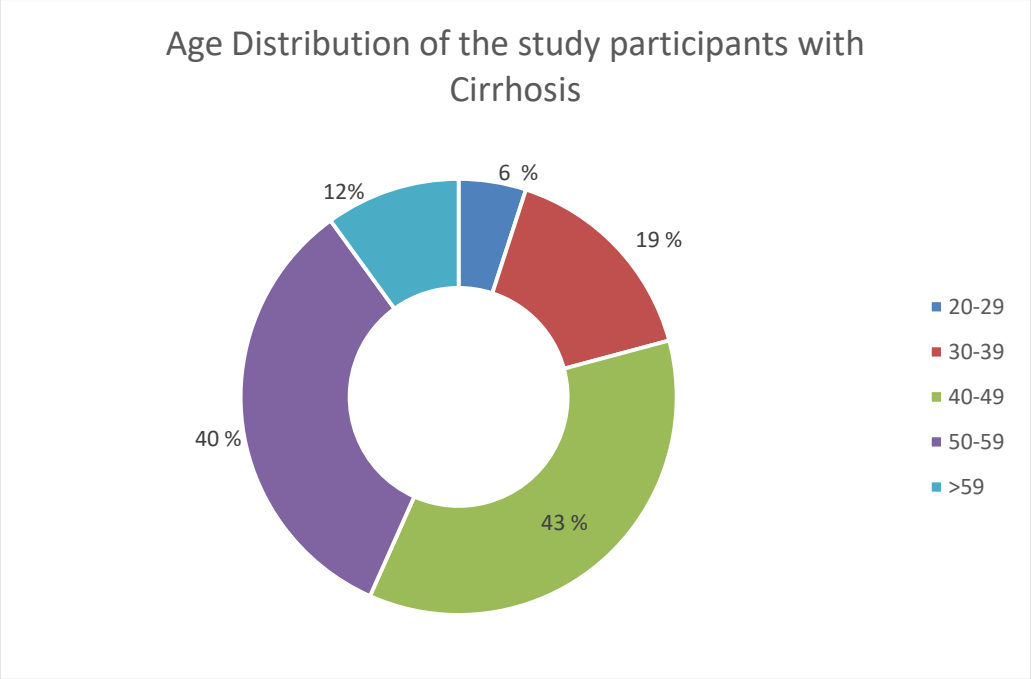
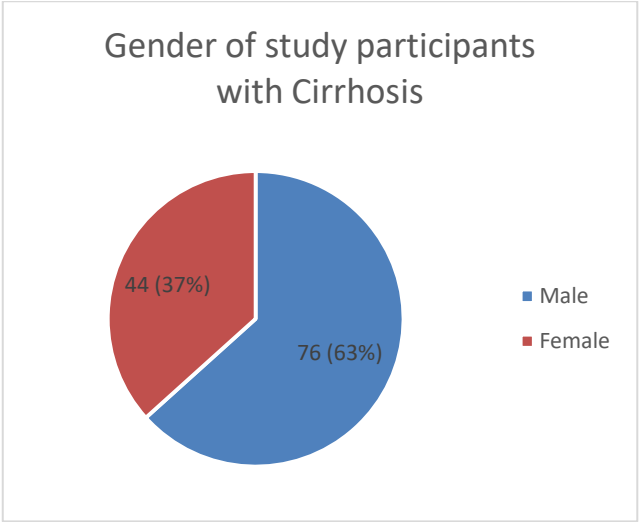


TABLE 2: SEX DISTRIBUTAION

SEX	NO OF PATIENTS	PERCENTAGE
MALE	76	63%
FEMALE	44	37%



In this study males (76) which is 63% and females of (44) 37% were studied,

TABLE 3: ASCITES

Ascites	NO OF PATIENTS	PERCENTAGE
Yes	98	82%
No	22	18%

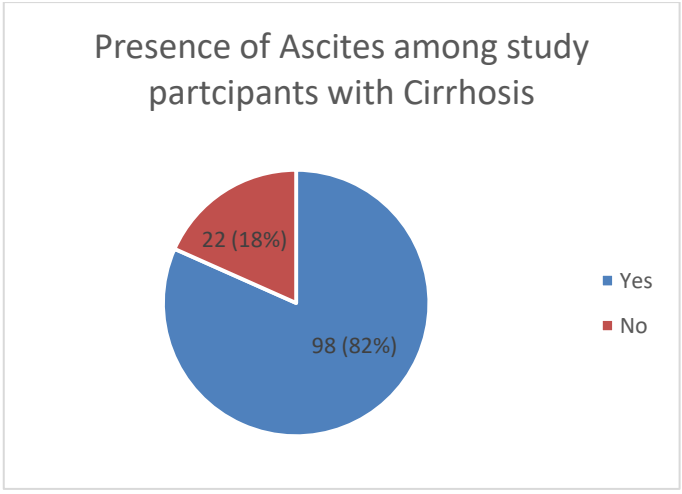


TABLE 4: UPPER GASTROINTESTINAL BLEEDING

UGI Bleeding	NO OF PATIENTS	PERCENTAGE
Yes	29	24%
No	91	76%

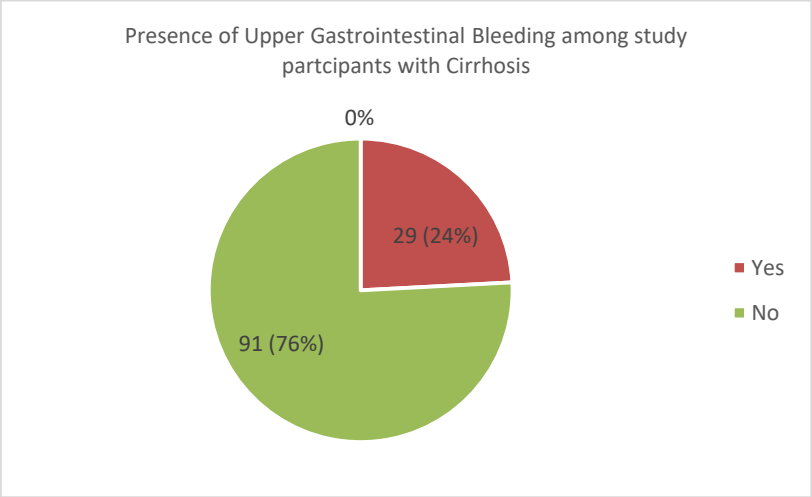


TABLE 5: ENCEPHALOPATHY

Encephalopathy	NO OF PATIENTS	PERCENTAGE
Yes	23	19%
No	97	81%

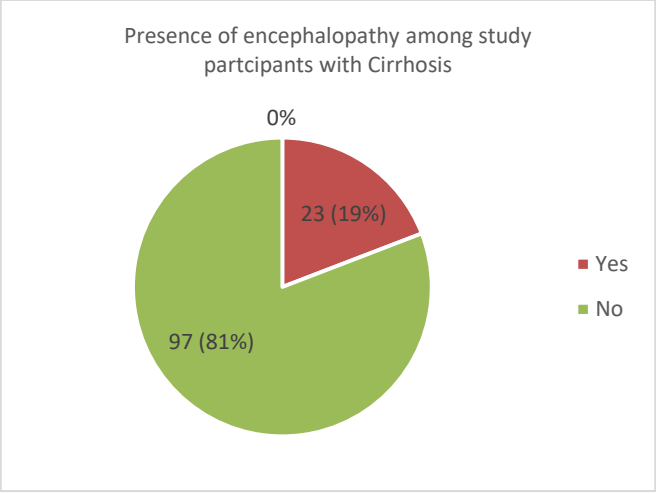


TABLE 6: SBP

SBP	NO OF PATIENTS	PERCENTAGE
Yes	23	19%
No	97	81%

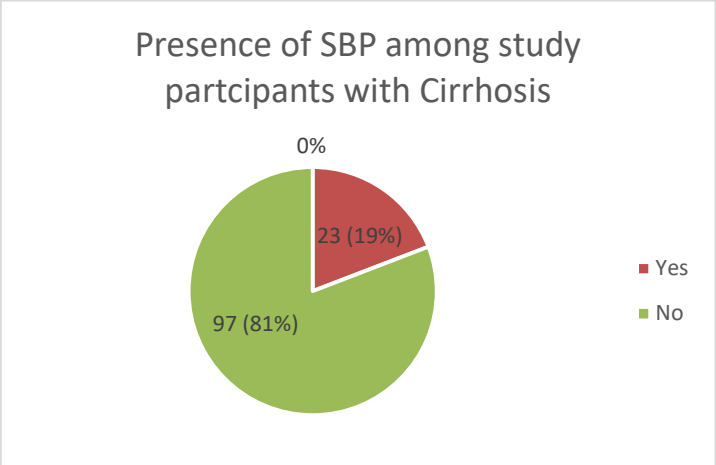


TABLE 7: HEPATORENAL SYNDROME

Hepatorenal Syndrome	NO OF PATIENTS	PERCENTAGE
Yes	13	11%
No	107	89%

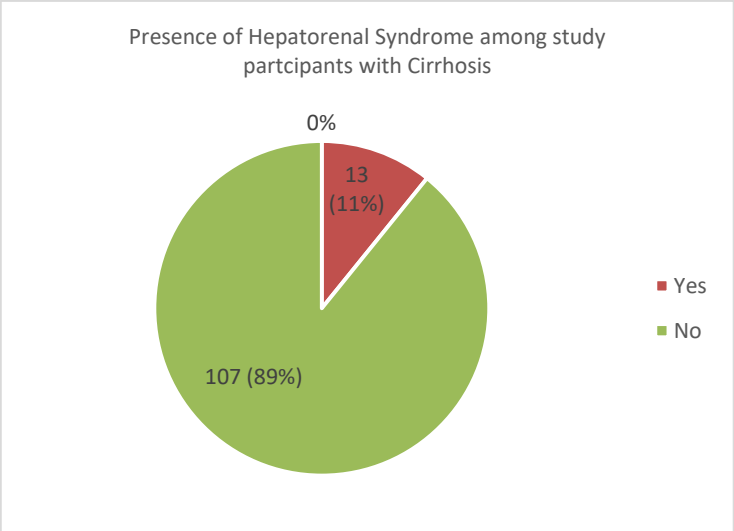


TABLE 8 : HEPATOPULMONARY SYNDROME

Hepatopulmonary Syndrome	NO OF PATIENTS	PERCENTAGE
Yes	3	2%
No	117	98%

TABLE 9 : CHILD PUGH SCORE

Child Pugh Score	NO OF PATIENTS	PERCENTAGE
A	44	36.7
B	50	41.7
C	26	21.7

In my study among total of 120 patients , 44 patients were under the child pugh score category A (36.7%), 50 comes under category B (41.7%), 26 comes under category C(21.7%).

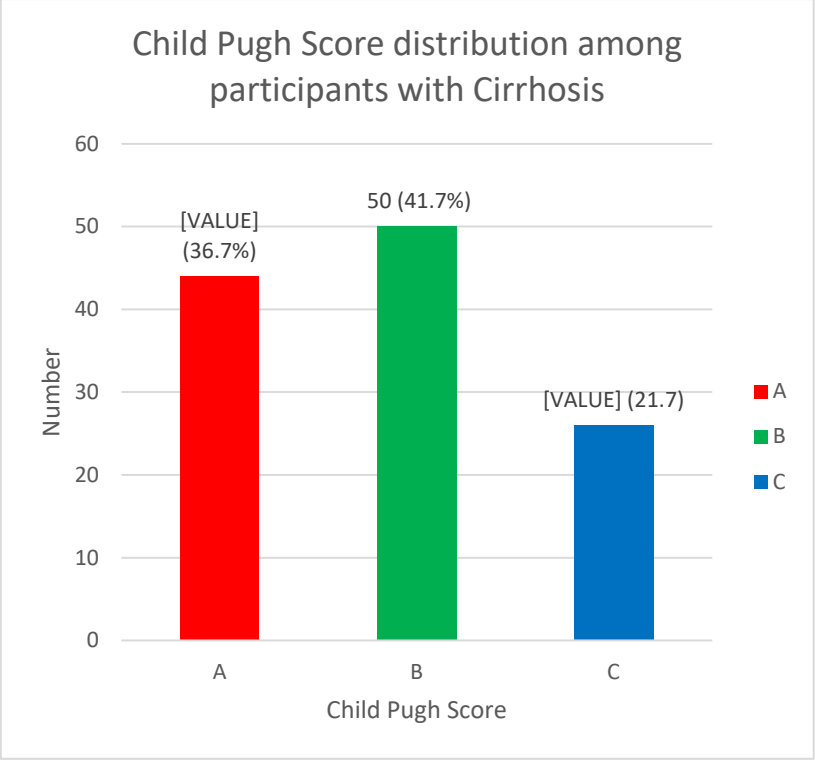


TABLE 10 : MELD SCORE

MELD Score	NO OF PATIENTS	PERCENTAGE
1 to 10	4	3.3
11 to 18	16	13.3
19 to 24	37	30.8
>24	63	52.5

In this study mean MELD score was 26.1 with the SD of 8.4. It ranges from 10-50

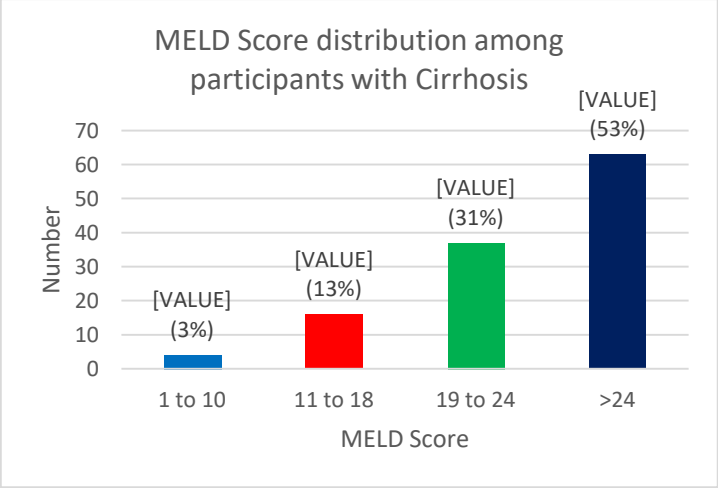


TABLE 11: ETIOLOGY OF CIRRHOSIS

Etiology	NO OF PATIENTS	PERCENTAGE
Alcoholic	84	75.0
Hepatitis B	8	7.1
NASH	6	5.4
Cryptogenic	3	2.7
Heart Failure	3	2.7
EHPVO	2	1.8
HCC	2	1.8
Autoimmune hepatitis	1	0.9
Wilson disease	1	0.9
Budd Chiari Syndrome	1	0.9
Primary biliary Cirrhosis	1	0.9

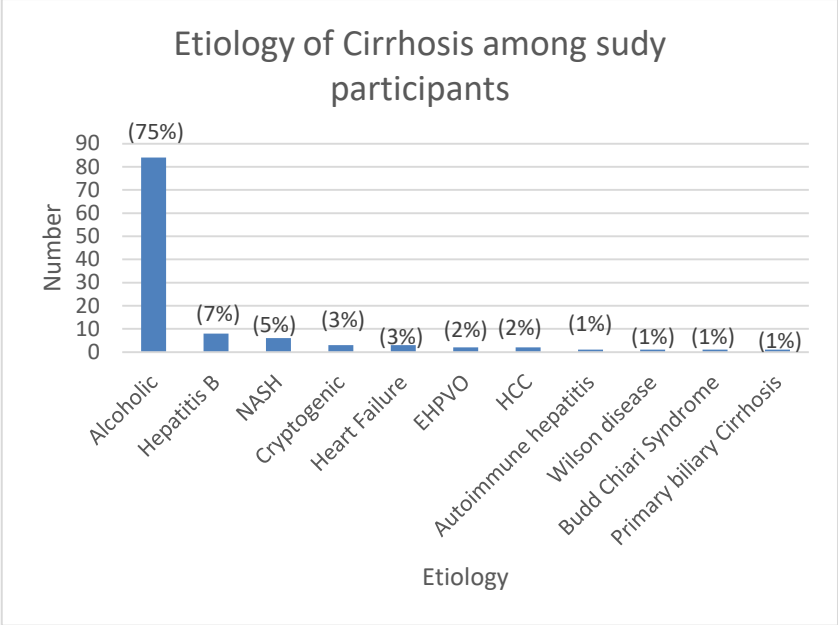


TABLE 12: TREATMENT OUTCOME

Treatment Outcome	NO OF PATIENTS	PERCENTAGE
Live	115	95.8
Dead	5	4.2

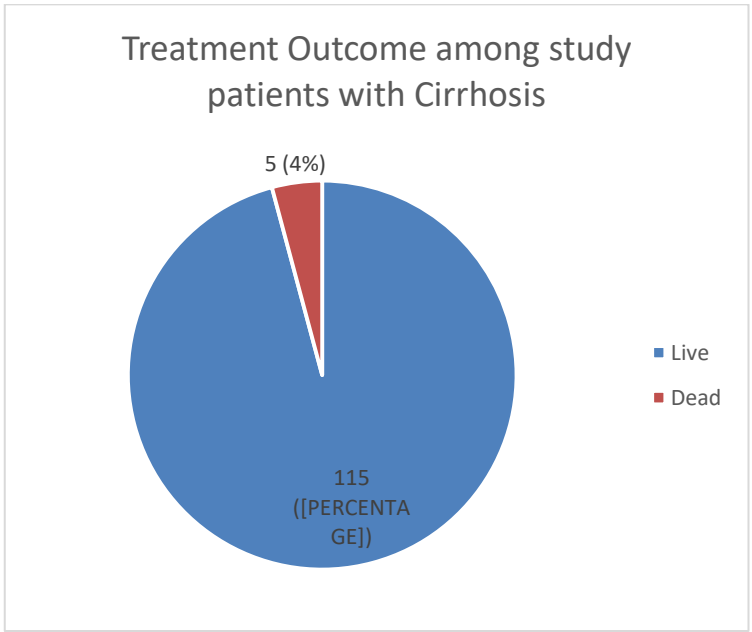


TABLE 13: LIPID PROFILE ACCORDING TO CHILD PUGH SCORE CLASSIFICTION

Lipid Profile characteristics		**Child Pugh Score**		
		A (n-44)	**B (n-50)**	**C (n-26)**
Cholesterol	Mean±SD	176.9 (12.0)	148.6 (11.8)	121.4 (9.5)
	Range	152-210	130-178	102-134
	95% Confidence interval	173.2-180.5	145.3-152.0	117.6-125.3
	P value (Anova)	<0.001		
Triglyceride	Mean±SD	152.1 (9.0)	130.1 (8.6)	92.7 (9.9)
	Range	125-174	110-145	74-112
	95% Confidence interval	149.3-154.8	127.7-132.6	88.7-96.7
	P value (Anova)	<0.001		
LDL	Mean±SD	101.5 (12.4)	86.6 (10.9)	74.3 (10.3)
	Range	77-140.6	69.6-116	57.6-94.4
	95% Confidence interval	97.7-105.3	83.5-89.7	70.1-78.5
	P value (Anova)	<0.001		
VLDL	Mean±SD	30.4 (1.8)	26.0 (1.7)	18.5 (2.0)
	Range	25-34.8	22-29	14.8-22.4
	95% Confidence interval	29.9-31.0	25.5-26.5	17.7-19.3
	P value (Anova)	<0.001		
HDL	Mean±SD	45.0 (5.2)	36.0 (4.7)	28.6 (4.3)
	Range	34-55	28-45	22-37
	95% Confidence interval	43.4-46.5	34.7-37.3	26.8-30.3
	P value (Anova)	<0.001		

In my study depending on the child pugh score lipid profile changes has been depicted. Cholesterol level found to be lowest in child pugh category C when compared to child pugh score B then to A, with the mean value of 176.9±12 in group A, 148.6±11.8 in group B and 121.4±9.5 in group3+ C. it is found statistically significant with the P value <0.001.

The triglyceride values were found statistically significant with mean value of 152±9 in group A, 130±8.6 in group B and 92.7±9.9 in group C with P value of <0.001.

The serum LDL levels were calculated, mean value of 101.5±12.4 in group A, 86.6±10.9 in group B and 74±10.3 in group C, found statistically significant.

The serum VLDL values were calculated mean values are 30.4±1.8 (group A), 26±1.7 (group B) and 18.2±2.0 (group C), which are statistically significant.

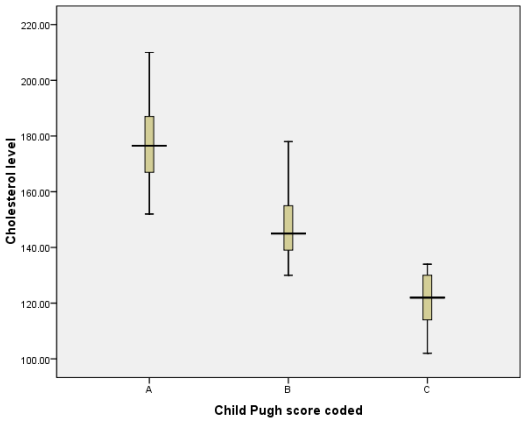
The serum HDL values are measured with mean values of 45±5.2 in group A, 36±4.7 in group B and 28.6±4.3 in group C which are statistically significant with P value of <0.001.

TABLE 14; LIPID PROFILE DEPENDS ON MELD SCORE

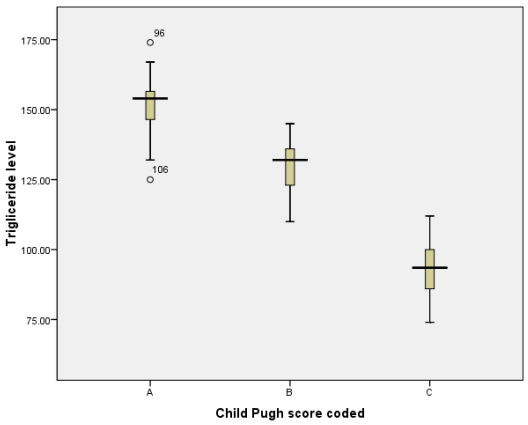
Lipid Profile characteristics		**MELD Score**			
		≤10 (n-4)	**11-18 (n-16)**	**19-24 (n-37)**	**>24 (n-63)**
Cholesterol	Mean±SD	165.0 (18.7)	170.1 (18.5)	164.8 (18.0)	141.1 (22.0)
	Range	143-188	130-188	134-210	102-192
	95% Confidence interval	135.2-194.8	160.3-180.0	158.8-170.8	135.6-146.7
	P value (Anova)	<0.001			
Triglyceride	Mean±SD	143.3 (16.8)	143.8(15.5)	143.6 (13.7)	117.8 (24.1)
	Range	123-158	112-167	121-174	74-162
	95% Confidence interval	116.6-169.9	135.5-152.1	139.0-148.2	111.7-123.8
	P value (Anova)	<0.001			
LDL	Mean±SD	94.9 (9.6)	99.3 (12.5)	94.5 (14.9)	83.6 (14.2)
	Range	85.4-107.4	75.6-116	69.6-140.6	57.6-114.2
	95% Confidence interval	79.6-110.1	92.6-106.0	89.5-99.4	80.0-87.1
	P value (Anova)	<0.001			
VLDL	Mean±SD	28.7 (3.4)	28.8 (3.1)	28.7 (2.7)	23.6 (4.8)
	Range	24.6-31.6	22.4-33.4	24.2-34.8	14.8-32.4
	95% Confidence interval	23.3-34.0	27.1-30.4	27.8-29.6	22.3-24.8
	P value (Anova)	<0.001			
HDL	Mean±SD	41.5 (6.6)	42.1 (7.4)	41.6 (6.6)	34.0 (7.0)
	Range	33-49	28-54	28-55	22-54
	95% Confidence interval	31.0-52.0	38.1-46.0	39.4-43.8	32.2-35.8
	P value (Anova)	<0.001			

The mean values of serum total cholesterol, LDL, VLDL, HDL, triglycerides were found progressively decreased as the MELD score increases. This was found statistically significant with the P value of <0.001.

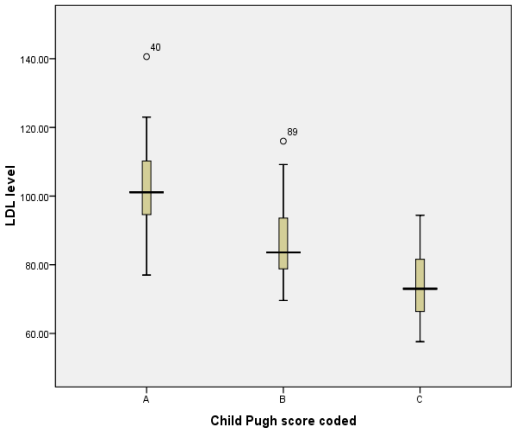
Cholesterol level



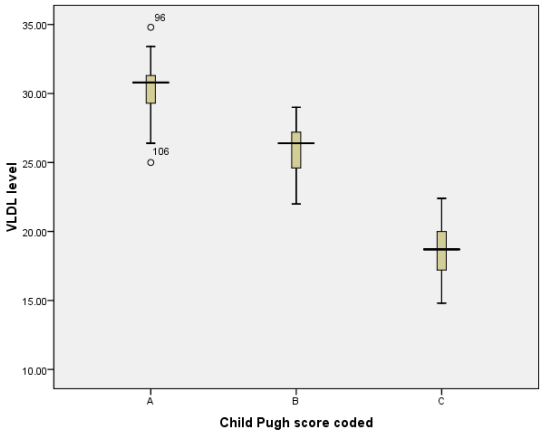
Triglyceride level



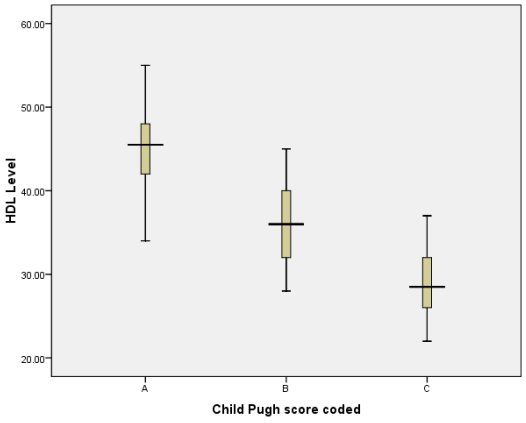
LDL level



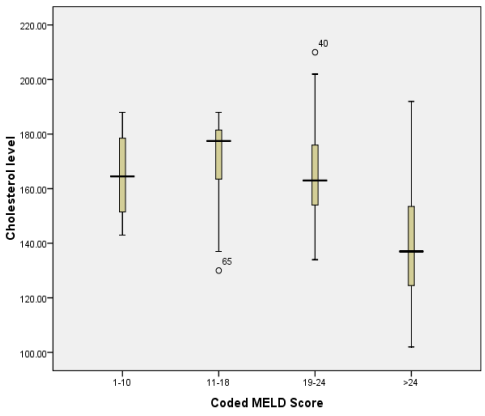
VLDL level



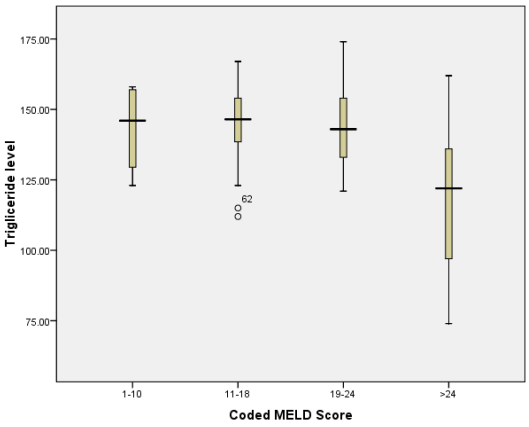
HDL Level



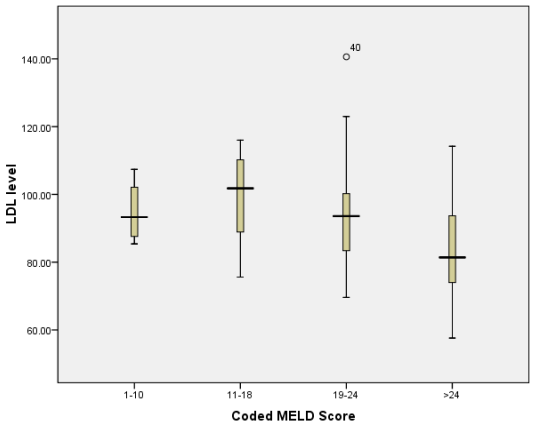
Cholesterol level



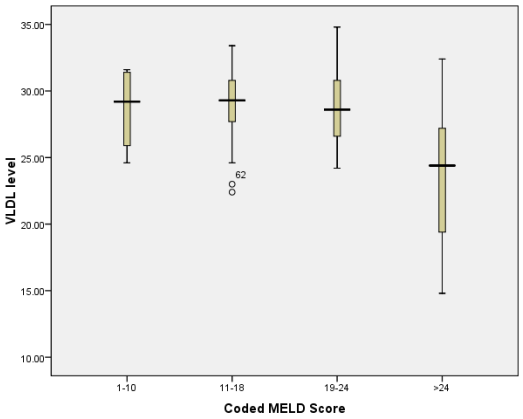
Triglyceride level



LDL level



VLDL level



HDL Level

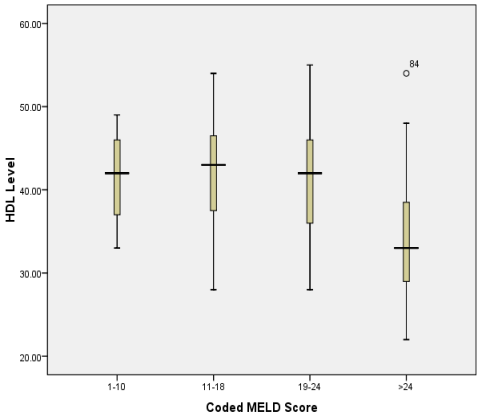


TABLE 15: GENDER WISE DISTRIBUTION OF LIPID PROFILE CHARACTERISTICS

Lipid Profile characteristics		Gender		
		Male (n-76)	Female (n-44)	P value*
Cholesterol	Mean±SD	152.9 (23.0)	153.4 (26.3)	0.91
Triglyceride	Mean±SD	130.6 (23.1)	129.1 (25.1)	0.73
LDL	Mean±SD	89.4 (14.3)	89.4 (17.1)	0.99
VLDL	Mean±SD	26.1 (4.6)	25.8 (5.0)	0.73
HDL	Mean±SD	37.4 (7.9)	38.2 (7.9)	0.59

*independent t test

TABLE 16: AGEWISE DISTRIBUTION OF LIPID PROFILE CHARACTERISTICS

Lipid Profile characteristics		Age group					
		20-29 (n-6)	30-39 (n-19)	40-49 (n-43)	50-59 (n-40)	>59 (n-12)	P value*
Cholesterol	Mean±SD	161.0 (17.9)	150.4 (21.6)	151.5 (23.3)	156.1 (27.1)	149.0 (20.2)	0.73
Triglyceride	Mean±SD	139.4 (24.7)	130.6 (22.6)	127.4 (23.4)	132.1 (24.6)	127.3 (25.8)	0.76
LDL	Mean±SD	95.1 (10.1)	87.7 (12.7)	89.1 (14.5)	90.1 (18.5)	87.8 (13.3)	0.86
VLDL	Mean±SD	27.9 (4.9)	26.1 (4.5)	25.5 (4.7)	26.4 (4.9)	25.5 (5.2)	0.76
HDL	Mean±SD	38.0 (7.0)	36.6 (8.3)	36.9 (9.0)	39.5 (6.7)	35.8 (6.5)	0.47

*ANOVA

TABLE 17: PRESENCE OF ASCITES AND DISTRIBUTION OF LIPID PROFILE CHARACTERISTICS

Lipid Profile characteristics		Ascites		
		Yes (n-98)	No (n-22)	P value*
Cholesterol	Mean±SD	150.3 (22.6)	165.4 (25.4)	0.007
Triglyceride	Mean±SD	129.1 (24.0)	134.2 (22.7)	0.365
LDL	Mean±SD	87.5 (14.9)	97.7 (14.8)	0.005
VLDL	Mean±SD	25.8 (4.8)	26.8 (4.5)	0.365
HDL	Mean±SD	36.9 (7.6)	40.9 (8.2)	0.032

*independent t test

TABLE 18: PRESENCE OF UGI BLEEDING AND DISTRIBUTION OF LIPID PROFILE CHARACTERISTICS

Lipid Profile characteristics		UGI Bleeding		
		Yes (n-29)	No (n-91)	P value*
Cholesterol	Mean±SD	154.7 (26.3)	152.5 (23.0)	0.671
Triglyceride	Mean±SD	130.9 (24.3)	129.8 (23.7)	0.821
LDL	Mean±SD	89.8 (15.4)	89.3 (15.4)	0.856
VLDL	Mean±SD	26.2 (4.8)	25.9 (4.7)	0.821
HDL	Mean±SD	38.7 (7.8)	37.4 (7.9)	0.426

*independent t test

TABLE 19: PRESENCE OF SBP AND DISTRIBUTION OF LIPID PROFILE CHARACTERISTICS

Lipid Profile characteristics		SBP		
		Yes (n-23)	No (n-97)	P value*
Cholesterol	Mean±SD	142.5 (21.0)	155.6 (23.8)	0.017
Triglyceride	Mean±SD	124.0 (25.3)	131.5 (23.3)	0.178
LDL	Mean±SD	83.0 (11.7)	90.9 (15.7)	0.025
VLDL	Mean±SD	24.8 (5.1)	26.3 (4.7)	0.178
HDL	Mean±SD	34.7 (8.4)	38.4 (7.6)	0.045

*independent t test

TABLE 20: SEX WISE DISTRIBUTION OF CHILD PUGH SCORE

Sex	Child Pugh Score			
	A (n-44)	B (n-50)	C (n-26)	P value*
Male	30 (68.2)	29 (58.0)	17 (65.4)	0.58
Female	14 (31.8)	21 (42.0)	9 (34.6)	

*Chi square test

Figure: Sexwise distribution of Child Pugh Score

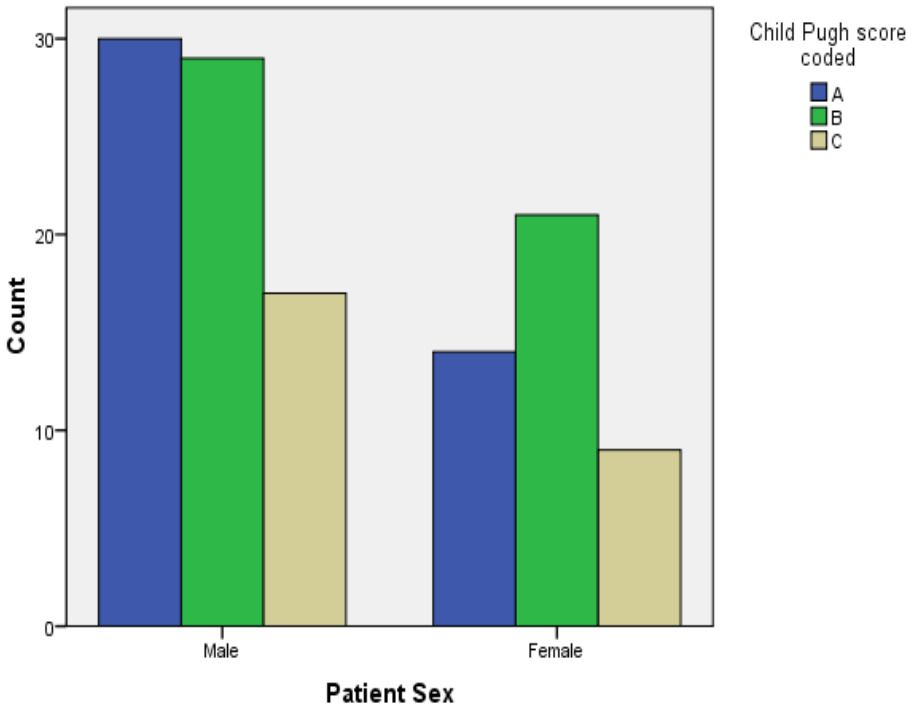


TABLE 21: CHILD PUGH SCORE DISTRIBUTION RELATED TO PRESENCE OF ASCITES

Presence of ascites	Child Pugh Score			
	A (n-44)	B (n-50)	C (n-26)	P value*
Yes	31 (70.5)	44 (88.0)	98 (81.7)	0.065
No	13 (29.5)	6 (12.0)	3 (11.5)	

*Fischer's Exact test

Figure: Child Pugh Score distribution related to presence of ascites

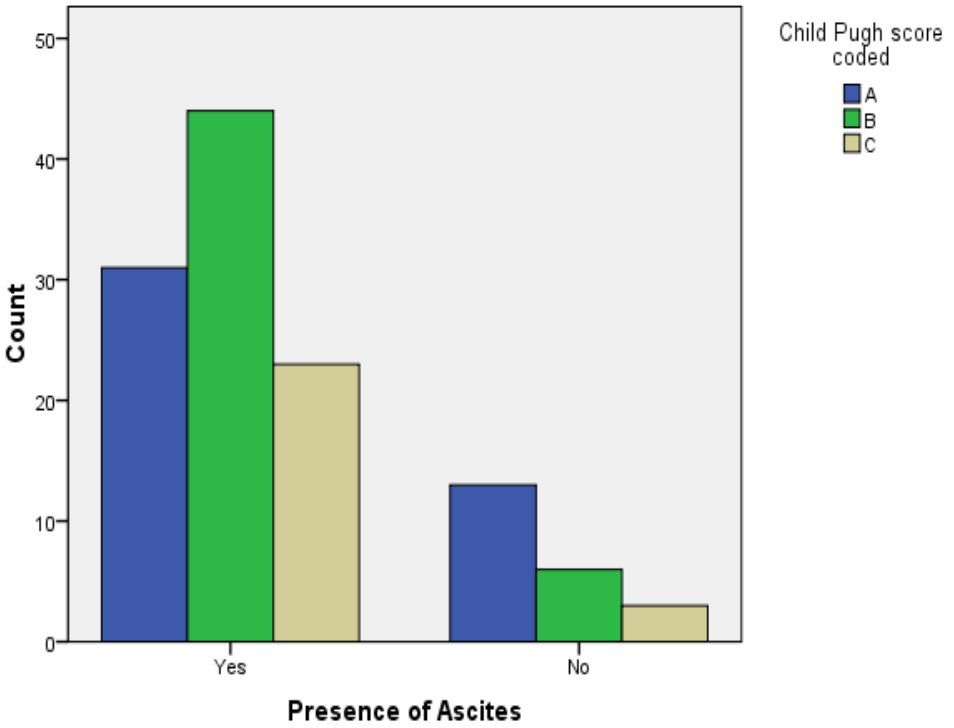


TABLE 22: CHILD PUGH SCORE DISTRIBUTION RELATED TO PRESENCE OF UGI BLEEDING

Presence of UGI Bleeding	Child Pugh Score			
	A (n-44)	B (n-50)	C (n-26)	P value*
Yes	15 (34.1)	7 (14.0)	7 (26.9)	0.071
No	29 (65.9)	43 (86.0)	19 (73.1)	

*Chi square test

Figure: Child Pugh Score distribution related to presence of UGI Bleeding

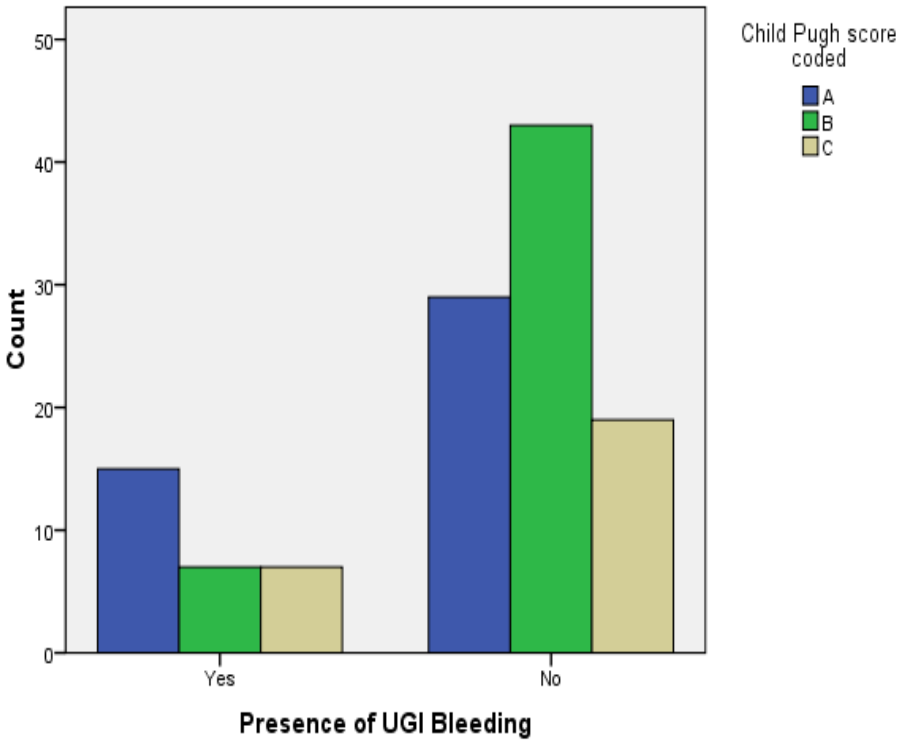


TABLE 23: CHILD PUGH SCORE DISTRIBUTION RELATED TO PRESENCE OF ENCEPHALOPATHY

Presence of encephalopathy	Child Pugh Score			
	A (n-44)	B (n-50)	C (n-26)	P value*
Yes	0 (0)	4 (8.0)	19 (73.1)	<0.001
No	44 (100)	46 (92.0)	7 (26.9)	

*Fischer's exact test

Figure: Child Pugh Score distribution related to presence of encephalopathy

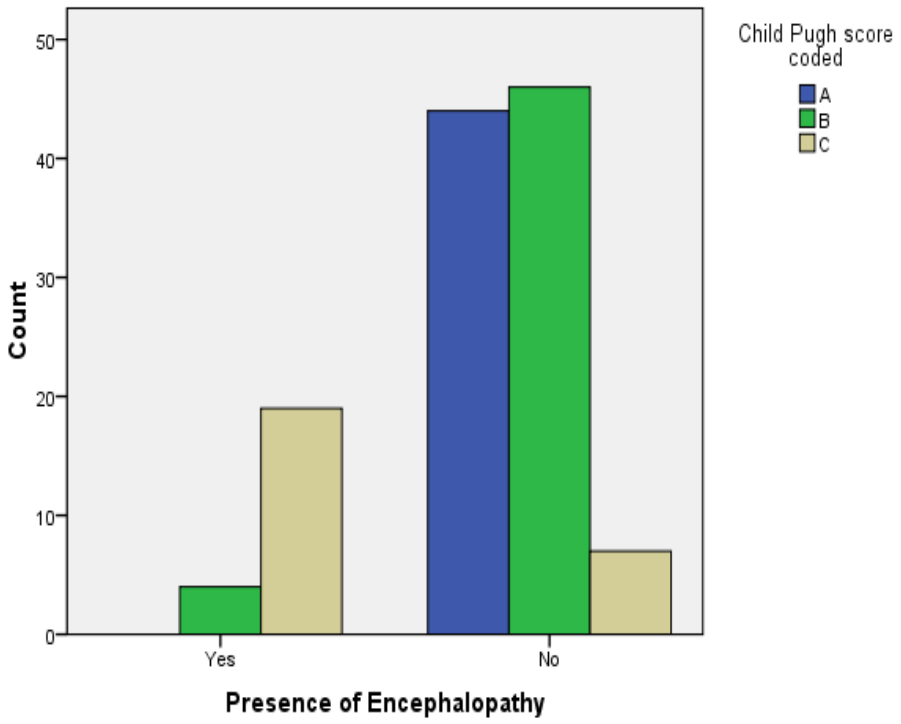


TABLE 24: CHILD PUGH SCORE DISTRIBUTION RELATED TO PRESENCE OF SBP

Presence of SBP	Child Pugh Score			
	A (n-44)	B (n-50)	C (n-26)	P value*
Yes	6 (13.6)	9 (18.0)	8 (30.8)	<0.21
No	38 (86.4)	41 (82.0)	18 (69.2)	

*Fischer's exact test

Figure: Child Pugh Score distribution related to presence of SBP

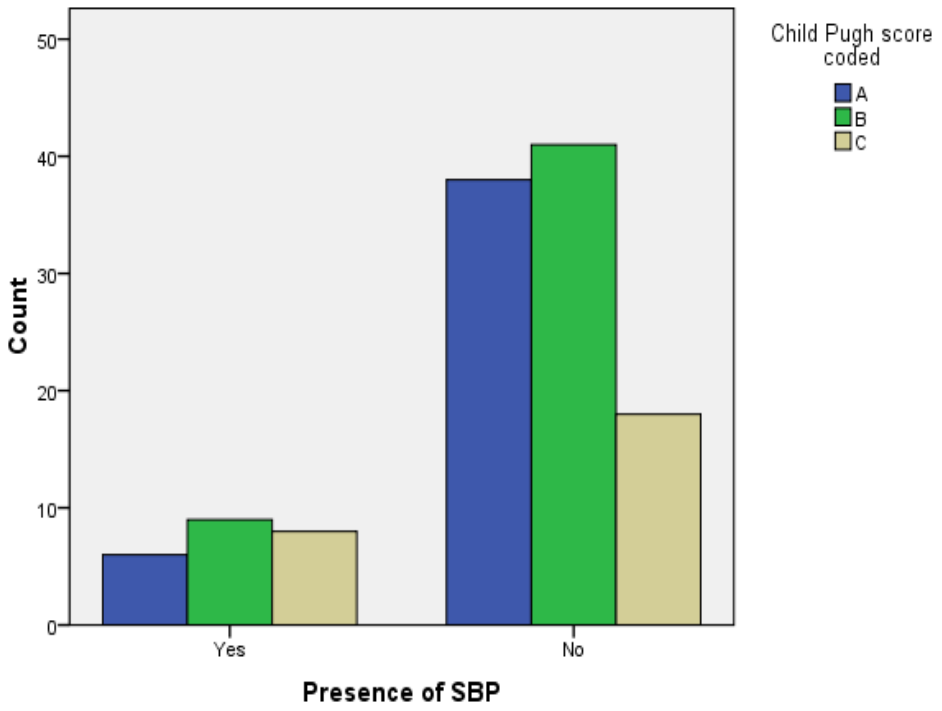


TABLE 25: CHILD PUGH SCORE DISTRIBUTION RELATED TO PRESENCE OF HEPATOPULMONARY SYNDROME

Presence of Hepatopulmonary syndrome	Child Pugh Score			
	A (n-44)	B (n-50)	C (n-26)	P value*
Yes	0 (0)	5 (10.0)	8 (30.8)	<0.001
No	44 (100)	45 (90.0)	18 (69.2)	

*Fischer's exact test

Figure: Child Pugh Score distribution related to presence of Hepatopulmonary syndrome

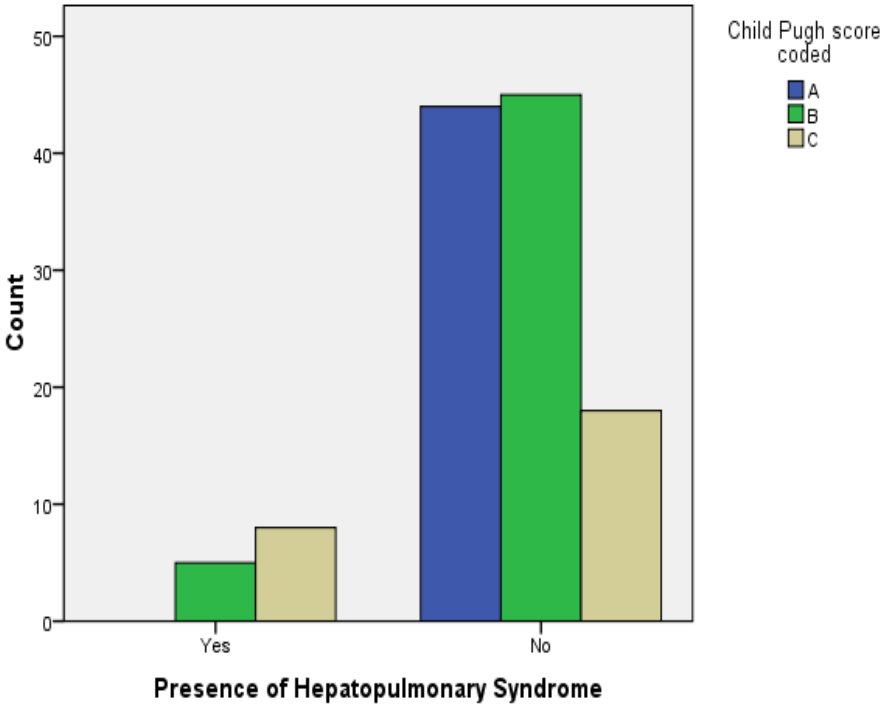


TABLE 26: CHILD PUGH SCORE DISTRIBUTION RELATED TO PRESENCE OF HEPATORENAL SYNDROME

Presence of Hepatorenal syndrome	Child Pugh Score			
	A (n-44)	B (n-50)	C (n-26)	P value*
Yes	0 (0)	0 (0)	3 (11.5)	0.009
No	44 (100)	50 (100)	23 (88.5)	

*Fischer's exact test

Figure: Child Pugh Score distribution related to presence of Hepatorenal syndrome

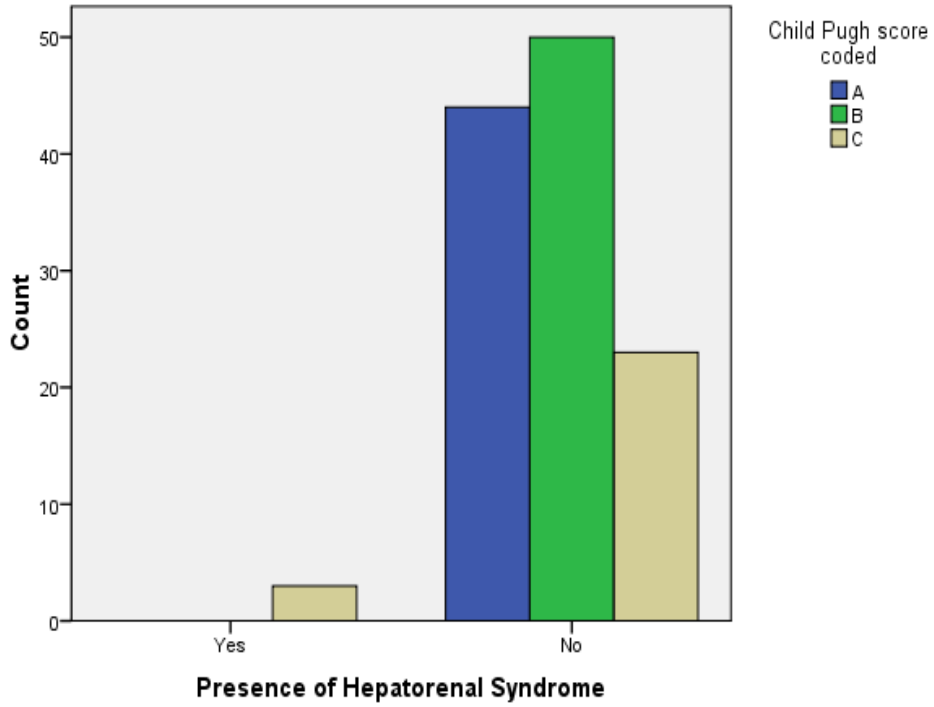


TABLE 27: SEX WISE DISTRIBUTION OF MELD SCORE

Sex	MELD score				
	≤10 (n-4)	11-18 (n-16)	19-24 (n-37)	>24 (63)	P value*
Male	2 (50.0)	10 (62.5)	22 (59.5)	42 (66.7)	0.81
Female	2 (50.0)	6 (37.5)	15 (40.5)	21 (33.3)	

*Fishcers' Exact test

Figure: Sexwise distribution of MELD Score

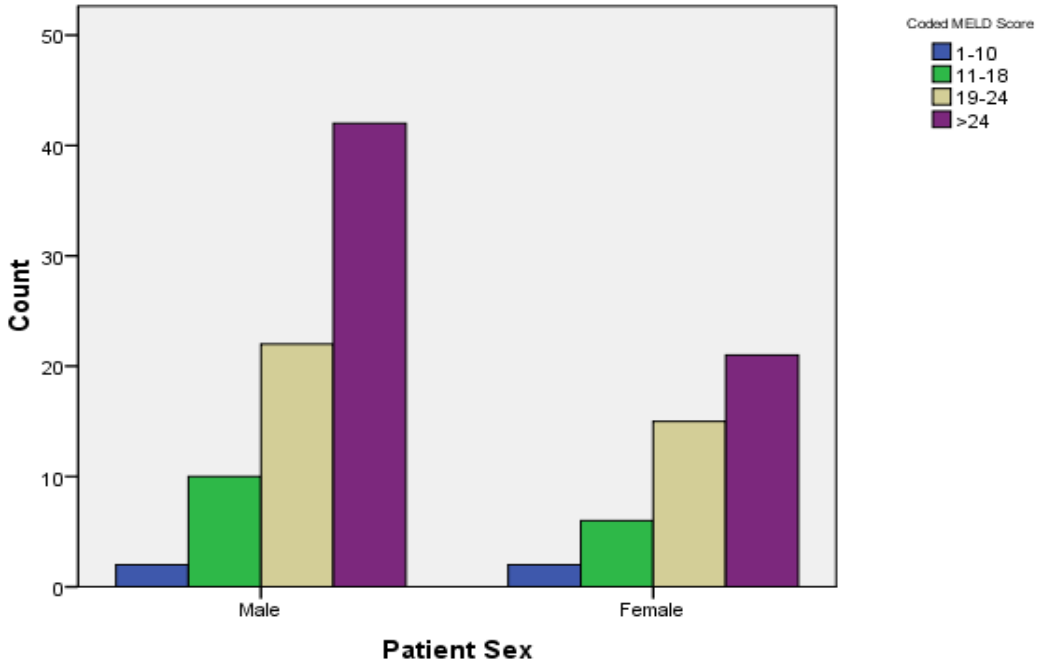


TABLE 28 : MELD SCORE DISTRIBUTION WITH PRESENCE OF UGI BLEEDING

Presence of UGI Bleeding	MELD score				
	≤10 (n-4)	11-18 (n-16)	19-24 (n-37)	>24 (63)	P value*
Yes	3 (75.0)	2 (12.5)	9 (24.3)	15 (23.8)	0.106
No	1 (25.0)	14 (87.5)	28 (75.7)	48 (76.2)	

*Fishcers' Exact test

Figure: MELD Score distribution with presence of UGI Bleeding

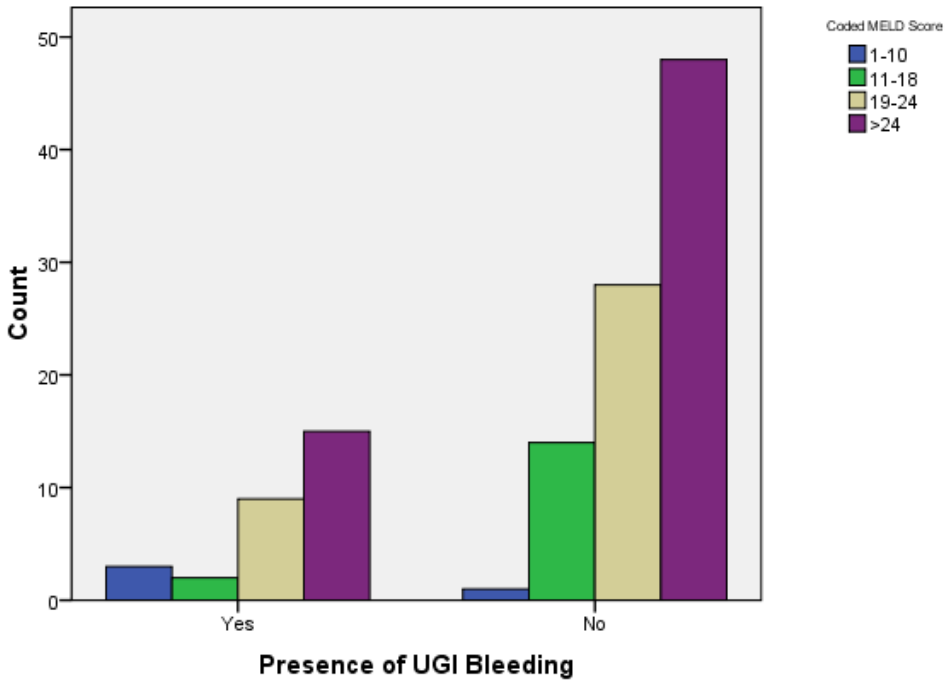


TABLE 29: MELD SCORE DISTRIBUTION WITH PRESENCE OF ENCEPHALOPATHY

Presence of encephalopathy	MELD score				
	≤10 (n-4)	11-18 (n-16)	19-24 (n-37)	>24 (63)	P value*
Yes	0 (0)	0 (0)	1 (2.7)	22 (34.9)	<0.001
No	4 (100)	16 (100)	36 (97.3)	41 (65.1)	

*Fishcers' Exact test

Figure: MELD Score distribution with presence of encephalopathy

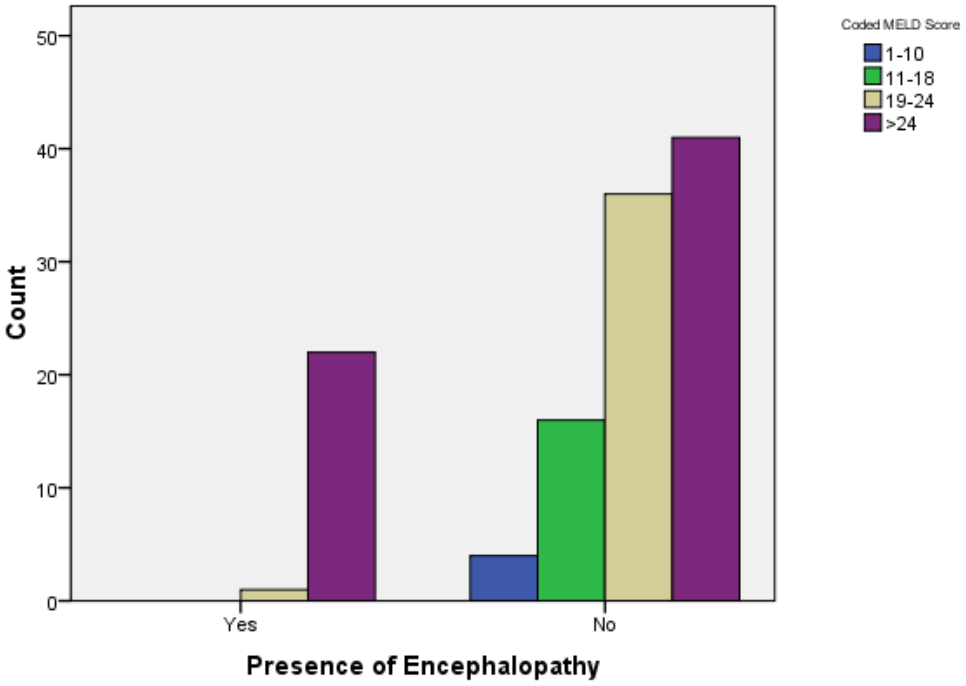


TABLE 30: MELD SCORE DISTRIBUTION WITH PRESENCE OF HEPATOPULMONARY SYNDROME

Presence of Hepatopulmonary syndrome	MELD score				
	≤10 (n-4)	11-18 (n-16)	19-24 (n-37)	>24 (63)	P value*
Yes	0 (0)	0 (0)	4 (10.8)	9 (14.3)	0.457
No	4 (100)	16 (100)	33 (89.2)	54 (85.7)	

*Fishcers' Exact test

Figure: MELD Score distribution with presence of Hepatopulmonary syndrome

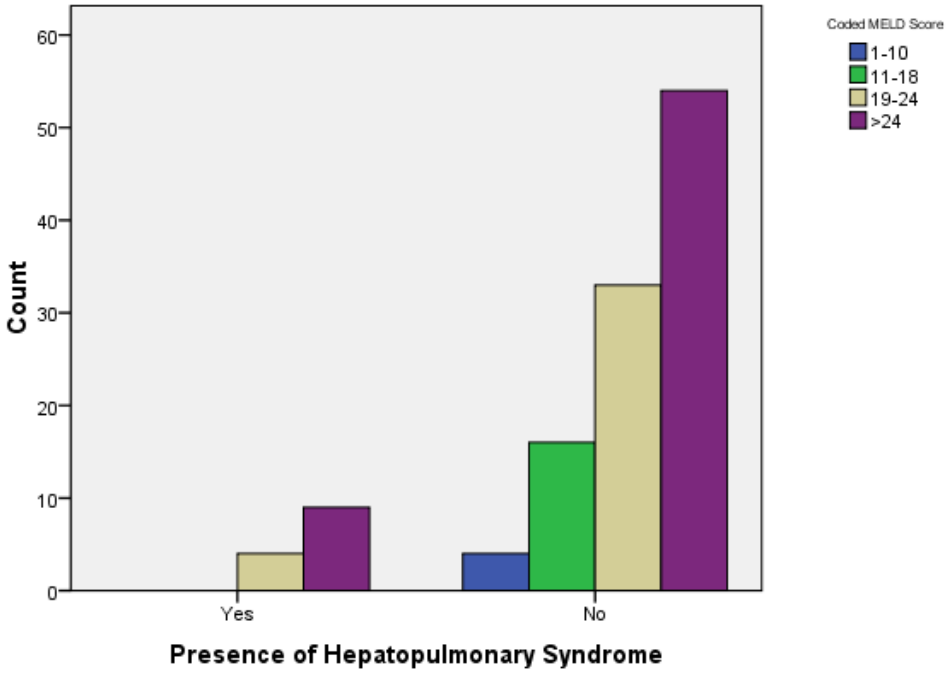
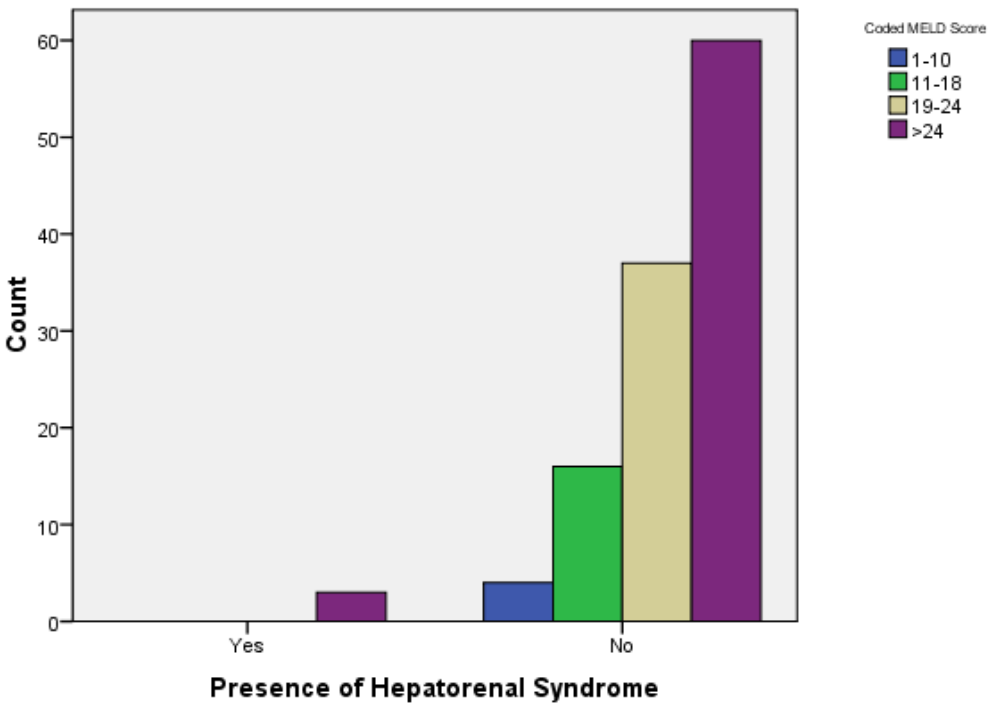


TABLE 31: MELD SCORE DISTRIBUTION WITH PRESENCE OF HEPATORENAL SYNDROME

Presence of Hepatorenal syndrome	MELD score				
	≤10 (n-4)	11-18 (n-16)	19-24 (n-37)	>24 (63)	P value*
Yes	0 (0)	0 (0)	0 (0)	3 (4.8)	0.593
No	4 (100)	16 (100)	37 (100)	60 (95.2)	

*Fishcers' Exact test

Figure: MELD Score distribution with presence of Hepatorenal syndrome



DISCUSSION

Dyslipidemia is frequent founding in cases of diabetes mellitus, cardiovascular disease, cerebrovascular disease, etc. Though they are studies predicting the lipid profile changes in cirrhosis patients, they found to be less in number in our Tamilnadu. Since the case load in our Coimbatore medical college hospital is surplus, we had interest in depicting the lipid profile changes in cirrhosis and considering this as a newly added prognostic indicator in assessing the severity of cirrhosis.

We have selected 120 cases (males=76; females=44) of cirrhosis diagnosed using clinical features like jaundice, ascites, upper gastrointestinal bleed, hepatic encephalopathy, hepatorenal syndrome, etc confirmed by biochemical tests i.e complete blood count, liver function tests, coagulation profile and tests towards the etiology of cirrhosis like viral markers, serum ceruloplasmin, ANA profile, serum iron studies. Further those patients were imaged by ultrasonogram of abdomen and proceeded with oesophagogastroduodeno scopy for varices.

Results were consistent with previous studies. In our study, we found that parameters like serum total cholesterol, LDL, VLDL, HDL, triglycerides were significantly lower as the stage of severity of cirrhosis advances. Fazl subhan, Imran khan et al conducted similar study in which they have concluded that serum cholesterol, LDL, HDL were significantly reduced in patients with cirrhosis in comparison with control, where TGL levels were statistically not

significant. Serum cholesterol and other parameter significantly reduced as the synthetic function of liver is affected enormously in cirrhosis because of fibrosis and nodule formation.

In our study depending on the Child Pugh Turcott score lipid profile changes has been depicted. Cholesterol level found to be lowest in Child Pugh Turcott category C when compared to Child Pugh Turcott score B then to A, with the mean value of 176.9±12 in group A, 148.6±11.8 in group B and 121.4±9.5 in group3+ C. It is found statistically significant with the P value <0.001.

The triglyceride values were found statistically significant with mean value of 152±9 in group A, 130±8.6 in group B and 92.7±9.9 in group C with P value of <0.001.

The serum LDL levels were calculated, mean value of 101.5±12.4 in group A, 86.6±10.9 in group B and 74±10.3 in group C, found statistically significant.

The serum VLDL values were calculated mean values are 30.4±1.8 (group A), 26±1.7 (group B) and 18.2±2.0 (group C), which are statistically significant. The serum HDL values are measured with mean values of 45±5.2 in group A, 36±4.7 in group B and 28.6±4.3 in group C which are statistically significant with P value of <0.001.

Our study showed that, cholesterol level in more in Child grade A when compared to Child grade B in turn with grade C. Suman, Ramesh kumar,

Prabahar et al conducted similar study in Hyderabad showed serum cholesterol and LDL levels had high area under curve which statistically significant associated with cirrhosis severity. In that study they compared the results with healthy individuals.

In Suman et al study the most common cause of cirrhosis is of viral etiology. They also compared alcoholic cirrhosis with non-alcoholic cirrhosis patients. Total cholesterol mean value of 137mg/dl in Child C, LDL level was <75mg/dl.

One more study conducted in Kerala by Hasik, Mohammed et al concluded that mean values of serum total cholesterol, LDL, HDL, Triglycerides were significantly lower in Child Pugh grade C in comparison with other grades.

The decreased levels of LDL, HDL might be attributed to reduced synthesis of apolipoproteins A and B. Since the apo B is involved in synthesis of VLDL, the reduced level of triglycerides is explained in cirrhosis. This can be due to insulin resistance found in liver cirrhosis. Insulin signaling mechanism in cirrhosis is found critical for lipogenesis regulated by PI3K and AKT2 signaling pathways. Among the various transcription factors, sterol regulatory element binding protein-1c (SREBP-1c) has stimulatory effect on the genes involving in lipogenesis.

Insulin activates the lipogenesis pathway in liver by SREBP-1c signaling pathway. Because of increased number of insulin receptors in patients with cirrhosis changes in lipid profile are encountered. AKT2 which is involved in

hepatic lipid accumulation explains one of the etiological factors of fatty liver. The pathophysiology of fatty liver first initiated by lipid accumulation followed by inflammation and oxidative stress. As the disease progresses from fibrosis to cirrhosis, the inflammatory process and oxidative stress are responsible for augmentation of insulin receptors.

The international monthly journal of hepatology December 2010 showed a significant decrease in levels of serum total cholesterol, LDL, HDL and triglycerides in cirrhosis as the severity increases.

The journal of Arab society for medical research 2012 depicted that the changes of lipid profile in cirrhosis patients irrespective of the incidence of hepatocellular carcinoma. The TGL levels and LDL levels are inversely related to the severity of cirrhosis and the changes are also correlated with hepatocellular carcinoma.

Our study lacks correlation of lipid profile abnormalities with complications of cirrhosis. Though the results are depicted significant with hepatorenal syndrome and hepatic encephalopathy.

Lipid profile abnormalities have well documented negative correlation with severity of cirrhosis. This study ensures that lipid profile abnormalities in cirrhosis as the synthetic function impaired in those patients. The correlation between complications of cirrhosis and lipid profile changes need further studies to be clarified. In near future as like Child Pugh Turcott score and MELD score lipid profile parameters can be included as an indicator of severity of cirrhosis.

Currently, cirrhosis is considered a dynamic disease able to progress and regress.in this new way of thinking the spectrum of changes characterizing chronic liver disease, early diagnosis and intervention is an important step to stop progression to decompensation and leads to high mortality. Step to arrest the progression to decompensation is an ominous step in the natural course of the disease. Transient elastography (Fibroscan) is an accurate non-invasive identification of patients who is having fibrosis progressing to cirrhosis by using score. Prevention or postponing the decompensation mainly by reducing the portal pressure by using long standing non selective beta blockers. Once the decompensation sets in, ultimate aim is to avoid further decompensation in the form of complications and reduce the mortality.

TIPS is effective in decreasing the risk of variceal bleeding and which improves the mortality in patients with recurrent ascites and refractory ascites. In few studies statins are associated with reduced incidence of HCC and hepatic portal venous pressure gradient. Role of Anticoagulants in cirrhosis is reserved for patients with portal vein thrombosis awaiting liver transplantation. Some clinical trails show not only reduced risk of portal vein thrombosis but also delayed decompensation and improved survival. Rifaximin is a potential alternative in prevention od SBP since it has lower bacterial resistance documented.

SUMMARY

- Cirrhosis is one of the commonest diseases worldwide.
- Fourteenth common cause of death worldwide, tenth most common cause of death in India as per world health organization. It may affect one in five Indians.
- Hepatocellular carcinoma is the second most common cause of death due to malignancy in world.
- There are various scoring system available to assess the severity of cirrhosis like Child Pugh Turcotte score includes serum bilirubin, ascites, encephalopathy, serum albumin and PT-INR. Model for end stage liver diseases (MELD) score also used for prioritizing patients for liver transplantation.
- Lipid metabolism is solely depend on liver. Hence, in cirrhosis the levels of lipid profile parameters like serum total cholesterol, LDL,VLDL, TGL, HDL are reduced with increasing severity of cirrhosis.
- Considering lipid profile abnormalities in chronic liver disease is paramount importance to assess the severity since the changes are correlating statistically significant with previously existing severity assessment score like Child Pugh Turcotte score and with the MELD score.
- Unlike other studies, in our study all the parameters of lipid profile namely, serum total cholesterol, serum HDL, triglycerides (measured by direct method), serum VLDL, LDL (calculated by formula) have been

found to be reduced with as the severity of cirrhosis increases. Lipid lowering drugs can be used in lower doses in cirrhotics.

- In a patient presenting with anasarca, evaluation of lipid profile can differentiate nephrotic patient from cirrhotics.
- In patients with cirrhosis and portal hypertension, the complications of cirrhosis has not found to be correlated with lipid profile abnormalities.
- However, hepatic encephalopathy and hepatorenal syndrome which were found to be significantly reduced in than patients without those complications.
- In patients with ascites total cholesterol and LDL are correlating well with increasing severity.

CONCLUSION

Lipid profile changes are common findings in patients with cirrhosis. In this study it was found that there is significant reduction in levels of lipid profile parameters like serum total cholesterol, LDL, VLDL, TGL, HDL in patients with cirrhosis as the severity increases. Presence of low lipid levels in cirrhosis patients presenting with altered sensorium and renal failure can aid in diagnosis of complications like hepatorenal syndrome and hepatic encephalopathy. Further formulation of scoring system in association with preexisting score system may provide better assessment of patients' prognosis in view of morbidity and mortality. Also it is cast effective method. We recommend it is necessary to assess fasting lipid profile in all patients with cirrhosis and prognosticate the disease progression.

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ANNEXURE - 1

PROFORMA

Name: IP No :

Age/Sex: DOA: D.O.D :

Religion: Hospital :

Address: Occupation :

I. PRESENTING COMPLAINTS:

1. Distention of abdomen
2. Swelling of lower limbs
3. Pain abdomen
4. Mass per abdomen
5. Fever
6. Yellowish discoloration of eyes
7. Altered sensorium
8. Dyspeptic symptoms
9. Loss of appetite /weight
10. Haemetamesis
11. Bleeding per rectum
12. Sleep disturbance

II. PAST HISTORY

a. Similar ailments like presenting symptoms

b. Previous hospitalization for similar complaints

c. History of Jaundice in the past

d. Blood transfusion

e. Intake of Hepatotoxic drugs

f. History of Immunization

g. Past history of any abdominal surgeries

h. Other illness

III. PERSONAL HISTORY

a. Diet : Veg./mixed

b. Sleep : Disturbed/undisturbed

c. Alcohol consumption : Duration

d. Bowel and bladder habits

IV. GENERAL PHYSICAL EXAMINATION

Built : Nourishment :

Scalp hair : Weight :

Skin : Height :

Conjunctiva : Sclera :

Oral cavity :

Neck : Lymph node enlargement : Yes / No

Thyroid enlargement : Yes / No

Parotid enlargement : Yes / No

Upper Limbs :

Flapping tremors

Dupytrens contracture

Palmar erythema

Spider Naevi

Oedema : Pitting / non pitting :

Jugular venous pulse :

Foetar hepaticus :

Anaemia :

Icterus :

Cyanosis :

Clubbing :

Lymph nodes :

Gynaecomastia :

Vital signs

Pulse/min : Blood pressure in mm Hg :

Temperature : Respiratory rate :

V. SYSTEMIC EXAMINATION:

I. ***Abdominal Examination:***

a. Inspection

Shape : Scaphoid/uniform distention

Umbilicus : Transverse/vertical eversion

Skin over the abdomen : Dry/tense/glistening

Dilatation of abdominal wall veins : Around umbilicus/Flanks

Movements of all quadrants of abdomen : Normal/Restricted

Visible persistalisis :

Scars and sinuses :

Hernial orifices :

External genetalia :

b. Palpation

Edema of the abdominal wall

Muscle guarding/rigidity

Tenderness

Abdominal girth at umbilical level

Liver : Palpable /Not

Size : Cms below right costal margin in mid clavicular line

Consistency : Soft/firm/hard

Surface : Smooth/Nodu1ar/Irregu1ar

Border : Sharp/Blunt

Tenderness : Present/Absent

Spleen : Palpable : Yes/No

Size : Cms below left costal margin in mid clavicular Line

Consistency : Soft/firm/hard

Tenderness : Present/Absent

Any other palpable mass :

Measurements of abdomen:

Abdominal girth at umbilicus :

Distance between umbilicus and pubic symphysis :

Distance between umbilicus and xiphisternum :

c. Percussion

Fluid thrill : Present/Absent

Shifting dullness : Present/Absent

Liver dullness : cms below right costal margin mid clavicular line

Splenic dullness : Present/Absent

d. Ausculitatiion

Over Liver : Rub/Bruit

Over spleen : Rub

Bowel sounds :

2. Cardio Vascular system examination

3. ***Respiratory system examination***

4. ***Central nervous system examination***

IX. INVESTIGATIONS

1. Routine Haematological examination

Hb gm% :

Total Count :

Differential count :

2. Urine analysis

Sugar : Albumin :

Microscopy : Bile salts/Bile pigments :

Urobilinogen :

3. Random blood sugar in mg/dl :

4. Blood urea in mg/dl :

5. Serum creatinine in mg/dl :

6. Liver function tests :

Serum total Billirubin :

Serum total proteins :

Serum Albumin :

Serum Globulin :

Albumin/Globulin ratio :

S.G.O.T :

S.G.P.T :

Serum Alkaline Phosphotase :

7. Lipid profile :

Tota cholesterol :

HDL :

LDL :

Triglyceride :

VLDL :

8.PT &INR :

8.ECG :

9.Ultrasound abdomen :

DIAGNOSIS

TREATMENT :

ANNEXURE - 2

CONSENT FORM

Yourself Mr./Mrs./Ms…….. are being asked to be a participant in the research study titled **A STUDY ON LIPID PROFILE AS AN INDICATOR OF SEVERITY IN CIRRHOSIS OF LIVER**" in CMC Hospital, Coimbatore, conducted by **Dr. Yamuna J,** Post Graduate Student, Department of General Medicine, Coimbatore Medical College. You are eligible after looking into the inclusion criteria. You can ask any question you may have before agreeing to participate.

Research Being Done

A study on lipid profile abnormalities in cirrhosis patients.

Purpose of Research

To investigate the lipid profile changes in patients with cirrhosis

Decline from Participation

You have the option to decline from participation in the study existing protocol for your condition.

Privacy and Confidentiality

Privacy of individuals will be respected and any information about you or provided by you during the study will be kept strictly confidential.

Authorization to publish Results

Results of the study may be published for scientific purposes and/or presented to scientific groups, however you will not be identified.

Statement of Consent

I volunteer and consent to participate in this study. I have read the consent or it has been read to me. The study has been fully explained to me, and I may ask questions at any time.

---------- ----------

Signature /Left thumb impression Date

(volunteer)

---------- ----------

Signature of witness Date

ஒப்புதல் படிவம்

பெயர் :

வயது :

பாலினம் :

முகவரி:

கோவை அரசு மருத்துவக்கல்லூரி மருத்துவமனையில் மருத்துவர் -தலைமையில் நடைபெறும் இந்த ஆய்வில் முழு சம்மதத்துடன் கலந்துகொள்ள சம்மதிக்கிறேன். இந்த ஆய்வில் என்னை பற்றி விவரங்களை பாதுகாப்புடன் இந்த ஆய்வில் வெளியிட ஆட்சேபணை இல்லை என்று தெரிவித்துக் கொள்கிறேன். எந்த நேரத்திலும் ஆய்வில் இருந்து எந்த நேரத்திலும் விலக்கிக்கொள்ளும் உரிமை உண்டு என்று அறிவேன்.

இடம் :

தேதி:

கைகெயாப்பம் /

ரேகை

ANNEXURE - 3

KEY TO MASTER CHART

SERIAL NUMBER

NAME

AGE

SEX

ASCITES – YES/NO

UGI BLEED- YES/NO

HEPATIC ENCEPHALOPATHY- YES/NO

SBP – YES/NO

HEPATORENAL SYNDROME- YES/NO

HEPATOPULMONARY SYNDROME- YES/NO

ETIOLOGY

CHILD PUGH SCORE – A (), B (), C ()

MELD SCORE

CHOLESTEROL

TRIGLYCERIDES

LDL

VLDL

HDL

OUTCOME

ANNEXURE - 4

Master Chart

S.NO	NAME	AGE	SEX	ASCITES	UGI BLEED	ENCEPHALOPATHY	SBP	HEPATORENAL SYNDROME	HEPATOPULMONARY SYNDROME	ETIOLOGY	CHILD PUGH SCORE	MELD SCORE	CHOLESTEROL	TRIGLYCERIDES	LDL	VLDL	HDL	OUTCOME
1	JEEVA	54	M	YES	NO	NO	YES	NO	NO	NASH	A	14	172	152	94.6	30.4	47	
2	FRANCIS	43	M	YES	NO	NO	NO	YES	NO	ALCOHOLIC	B	32	153	122	96.6	24.4	32	
3	PRABU	32	M	YES	NO	NO	YES	NO	NO	ALCOHOLIC	A	24	168	160	88	32	48	
4	SAROJINI	45	F	YES	NO	NO	YES	NO	NO	ALCOHOLIC	B	36	144	123	86.4	24.6	33	
5	RAJAN	48	M	YES	NO	NO	YES	NO	NO	HEPATITIS B	A	13	178	154	110.2	30.8	37	
6	KAMALA	57	F	YES	NO	NO	YES	NO	NO	HCC	B	19	139	132	81.6	26.4	31	
7	RAMASAMY	39	M	YES	NO	NO	NO	NO	NO	BUDD CHIARI SYNDROME	A	23	176	156	105.8	31.2	39	
8	NAGAMMAL	63	F	YES	NO	NO	NO	NO	NO	HEART FAILURE	B	23	143	134	78.2	26.8	38	
9	MOHAN	23	M	YES	NO	NO	NO	NO	NO	AUTOIMMUNE HEPATITIS	A	24	159	154	83.2	30.8	45	
10	RAJ	20	M	YES	NO	NO	NO	NO	NO	WILSONS DISEASE	B	25	156	143	93.4	28.6	34	
11	SUNDARAM	42	M	YES	NO	NO	NO	NO	NO	ALCOHOLIC	A	21	162	160	83	32	47	
12	SHANKAR	54	M	YES	YES	NO	NO	NO	NO	ALCOHOLIC	A	32	176	162	101.6	32.4	42	
13	VADIVU	46	F	YES	YES	NO	NO	NO	NO	ALCOHOLIC	B	28	142	136	75.8	27.2	39	
14	VIJAYA	52	F	YES	YES	NO	NO	NO	NO	NASH	B	29	138	128	81.4	25.6	31	
15	AANANDHI	27	F	YES	YES	NO	NO	NO	NO	CRYPTOGENIC	A	10	169	156	96.8	31.2	41	
16	VENKATASAMY	39	M	YES	NO	NO	NO	YES	NO	ALCOHOLIC	B	23	149	137	91.6	27.4	30	
17	BALAN	60	M	YES	NO	NO	NO	NO	NO	ALCOHOLIC	B	28	150	138	93.4	27.6	29	
18	MAYILSAMY	61	M	YES	NO	NO	NO	NO	YES	ALCOHOLIC	C	42	128	89	88.2	17.8	22	DEATH
19	KUMAR	48	M	YES	NO	YES	YES	NO	NO	ALCOHOLIC	C	30	130	102	81.6	20.4	28	

20	SELVARAJ	59	M	YES	NO	NO	YES	NO	NO	NASH	B	31	145	134	81.2	26.8	37	
21	AYYASAMY	38	M	YES	NO	YES	NO	NO	NO	ALCOHOLIC	C	35	121	98	71.4	19.6	30	
22	JAMEELA	40	F	YES	NO	NO	NO	YES	NO	ALCOHOLIC	B	21	136	122	69.6	24.4	42	
23	PICHAIYAMMAL	51	F	NO	YES	YES	NO	NO	NO	HEPATITIS B	C	33	112	88	66.4	17.6	28	
24	SELVAKUMAR	47	M	NO	YES	NO	NO	NO	NO	HEPATITIS C	A	21	176	154	99.2	30.8	46	
25	PALANIYAMMAL	52	F	NO	YES	YES	NO	NO	NO	ALCOHOLIC	B	20	155	122	90.6	24.4	40	
26	MOSES	52	M	YES	YES	YES	NO	YES	NO	ALCOHOLIC	C	36	122	100	70	20	32	
27	SELVI	59	F	YES	YES	NO	NO	NO	NO	NASH	A	18	188	154	111.2	30.8	46	
28	MURUGESAN	47	M	YES	NO	NO	NO	NO	NO	ALCOHOLIC	B	19	164	133	98.4	26.6	39	
29	VASUKI	51	F	YES	NO	NO	NO	NO	NO	ALCOHOLIC	B	25	154	140	84	28	42	
30	RAMANAN	34	M	YES	NO	YES	NO	NO	NO	ALCOHOLIC	B	27	136	132	81.6	26.4	28	
31	KANNAN	61	M	YES	NO	NO	NO	NO	NO	ALCOHOLIC	A	21	177	158	97.4	31.6	48	
32	SURESH	54	M	YES	NO	NO	NO	NO	NO	ALCOHOLIC	A	22	167	156	85.8	31.2	50	
33	KUPPUSAMY	31	M	YES	YES	NO	NO	NO	NO	PRIMARY BILIARY CIRRHOSIS	A	24	156	152	83.6	30.4	42	
34	JAYARAJ	47	M	YES	NO	YES	NO	YES	NO	ALCOHOLIC	C	34	132	110	88	22	22	
35	MARY	45	F	YES	NO	YES	NO	YES	NO	ALCOHOLIC	C	36	124	92	79.6	18.4	26	
36	ANBALAGI	50	F	YES	NO	YES	NO	NO	NO	ALCOHOLIC	C	38	108	74	59.2	14.8	34	
37	GOPALAKRISHNAN	56	M	NO	NO	NO	NO	NO	NO	ALCOHOLIC	B	31	172	135	102	27	43	
38	SUBBATHAL	62	F	YES	NO	NO	NO	NO	NO	HEART FAILURE	B	22	149	141	84.8	28.2	36	
39	KRISHNAN	54	M	YES	NO	NO	NO	NO	NO	ALCOHOLIC	A	26	192	154	113.2	30.8	48	
40	LALITHA	54	F	YES	NO	NO	NO	NO	NO	ALCOHOLIC	A	22	210	152	140.6	30.4	39	
41	GANESAN	38	M	YES	NO	NO	YES	NO	NO	ALCOHOLIC	B	34	133	123	80.4	24.6	28	
42	KRISHNAVENI	46	F	YES	NO	NO	YES	NO	NO	HEPATITIS B	C	35	104	82	57.6	16.4	30	
43	ARUMUGAM	54	M	YES	NO	NO	YES	NO	NO	ALCOHOLIC	A	37	152	145	77	29	46	
44	MOHANRAJ	36	M	YES	YES	YES	YES	NO	YES	ALCOHOLIC	C	50	112	98	66.4	19.6	26	DEATH
45	AYYANAR	32	M	YES	NO	NO	YES	NO	NO	ALCOHOLIC	C	33	132	86	86.8	17.2	28	
46	ALLWYN	54	M	YES	NO	NO	NO	NO	NO	ALCOHOLIC	B	24	148	136	78.8	27.2	42	

47	ELANGO	61	M	YES	YES	NO	NO	NO	NO	ALCOHOLIC	A	32	176	156	104.8	31.2	40	
48	BALAJI	65	M	YES	NO	NO	NO	NO	NO	NASH	A	22	166	158	98.4	31.6	36	
49	GOPINATH	35	M	YES	NO	NO	NO	YES	NO	ALCOHOLIC	B	21	142	132	80.6	26.4	35	
50	PECHIYAMMAL	48	F	YES	NO	NO	NO	NO	NO	ALCOHOLIC	A	32	166	155	97	31	38	
51	PRAKASH	49	M	YES	NO	NO	YES	NO	NO	ALCOHOLIC	B	12	137	123	84.4	24.6	28	
52	MEGALA	51	F	NO	NO	NO	NO	NO	NO	ALCOHOLIC	A	32	188	145	113	29	46	
53	SANTHOSH	51	M	YES	NO	NO	NO	NO	NO	HEPATITIS B	C	43	132	102	75.6	20.4	36	
54	KUMARI	49	F	YES	NO	NO	NO	NO	NO	ALCOHOLIC	B	23	155	134	83.2	26.8	45	
55	KUMAR	41	M	YES	NO	NO	NO	NO	NO	ALCOHOLIC	C	25	114	93	63.4	18.6	32	
56	SUSEELA	46	F	YES	NO	NO	NO	NO	NO	ALCOHOLIC	B	27	137	122	75.6	24.4	37	
57	VINOTH	58	M	YES	NO	NO	NO	NO	NO	ALCOHOLIC	B	29	135	132	69.6	26.4	39	
58	SELVAMANI	51	M	NO	YES	NO	NO	NO	NO	ALCOHOLIC	A	20	183	152	108.6	30.4	44	
59	RAMASAMI	52	M	NO	YES	NO	NO	NO	NO	ALCOHOLIC	B	32	142	121	85.8	24.2	32	
60	VASANTH	47	M	NO	YES	NO	NO	NO	NO	ALCOHOLIC	A	30	187	154	114.2	30.8	42	
61	SURYA	48	M	YES	NO	NO	NO	NO	NO	HEPATITIS B	A	21	166	149	100.2	29.8	36	
62	MANIYAN	50	M	YES	NO	NO	NO	NO	NO	ALCOHOLIC	B	13	143	115	82	23	38	
63	JAYAPAL	50	M	YES	NO	YES	NO	YES	NO	ALCOHOLIC	C	26	102	74	65.2	14.8	22	
64	JAYACHANDRAN	53	M	NO	YES	NO	NO	NO	NO	ALCOHOLIC	A	10	160	136	89.8	27.2	43	
65	BALAKRISHNAN	39	M	NO	YES	NO	NO	NO	NO	ALCOHOLIC	B	13	130	112	75.6	22.4	32	
66	GOVINDHASAMY	43	M	YES	NO	NO	NO	NO	NO	ALCOHOLIC	A	15	178	143	101.4	28.6	48	
67	MENAKA	45	F	NO	YES	YES	NO	NO	NO	ALCOHOLIC	C	36	119	94	72.2	18.8	28	
68	MICHEAL	29	M	NO	NO	NO	NO	NO	NO	ALCOHOLIC	A	15	177	148	108.4	29.6	39	
69	ABIRAMI	50	F	YES	NO	NO	NO	NO	NO	ALCOHOLIC	B	24	154	121	94.8	24.2	35	
70	KOLAPPAN	52	M	YES	NO	NO	YES	NO	NO	ALCOHOLIC	B	26	142	118	81.4	23.6	37	
71	SIVABHAGYAM	48	F	YES	NO	NO	YES	NO	YES	ALCOHOLIC	C	34	123	96	73.8	19.2	30	
72	KALAISELVI	43	F	YES	NO	NO	NO	NO	NO	NON ALCOHOLIC	B	27	144	132	77.6	26.4	40	
73	RANI	46	F	YES	NO	NO	NO	NO	NO	ALCOHOLIC	A	21	178	157	94.6	31.4	52	

74	RAJAMANI	38	M	YES	NO	NO	NO	NO	NO	ALCOHOLIC	B	22	152	138	83.4	27.6	41	
75	DEVI	61	F	YES	NO	YES	NO	YES	NO	ALCOHOLIC	C	41	125	84	71.2	16.8	37	
76	GIRIJA	47	M	YES	NO	NO	NO	NO	NO	ALCOHOLIC	A	15	171	143	96.4	28.6	46	
77	MARATHAL	47	F	YES	NO	NO	NO	NO	NO	HEPATITIS B	B	34	151	110	94	22	35	
78	PAULRAJ	24	M	YES	YES	YES	NO	NO	NO	ALCOHOLIC& SICKLE CELL DISEASE	C	26	129	90	85	18	26	
79	SUBBULAKSHMI	29	F	YES	NO	NO	NO	NO	NO	EHPVO	A	16	176	145	104	29	43	
80	AMAL	42	M	NO	YES	YES	NO	NO	NO	ALCOHOLIC	C	32	122	94	74.2	18.8	29	
81	ANTHONIYAMMAL	52	F	YES	NO	NO	NO	NO	NO	ALCOHOLIC	B	18	156	134	86.2	26.8	43	
82	ANTONY	38	M	YES	NO	YES	NO	YES	NO	EHPVO	C	35	133	102	79.6	20.4	33	
83	PAUL	45	M	NO	YES	NO	NO	NO	NO	ALCOHOLIC	A	24	187	132	115.6	26.4	45	
84	KIRISH	36	M	YES	NO	NO	NO	NO	NO	ALCOHOLIC	A	27	167	142	84.6	28.4	54	
85	KANNA	47	M	NO	YES	NO	NO	NO	NO	ALCOHOLIC	A	21	188	154	107.2	30.8	50	
86	ABDHUL	62	M	YES	NO	NO	NO	NO	NO	ALCOHOLIC	B	22	156	122	93.6	24.4	38	
87	JAFFER	61	M	NO	NO	NO	NO	NO	NO	ALCOHOLIC	B	36	165	126	104.8	25.2	35	
88	MARIYAPPAN	58	M	YES	NO	NO	NO	NO	NO	HEART FAILURE	A	14	188	158	114.4	31.6	42	
89	KANNAMAL	36	F	YES	NO	NO	NO	NO	NO	ALCOHOLIC	B	16	178	145	116	29	33	
90	CHELLAPAN	52	M	YES	NO	NO	NO	NO	NO	ALCOHOLIC	A	20	192	163	115.4	32.6	44	
91	CHELLAMAL	42	F	YES	NO	NO	NO	NO	NO	CRYPTOGENIC	B	24	163	129	109.2	25.8	28	
92	CHINNAPONNU	47	F	YES	NO	YES	NO	YES	NO	ALCOHOLIC	C	43	132	78	94.4	15.6	22	DEATH
93	MOIDEEN	51	M	YES	NO	NO	NO	NO	NO	ALCOHOLIC	A	22	186	145	123	29	34	
94	PODHUMPONNU	45	F	NO	NO	NO	NO	NO	NO	ALCOHOLIC	B	32	165	136	107.8	27.2	30	
95	IBRAHIM	55	M	YES	NO	NO	YES	NO	NO	ALCOHOLIC	B	32	145	126	83.8	25.2	36	
96	RANGI	53	F	NO	NO	NO	NO	NO	NO	ALCOHOLIC	A	21	202	174	112.2	34.8	55	
97	RATHNA	46	F	YES	NO	NO	YES	NO	NO	ALCOHOLIC	A	12	179	167	91.6	33.4	54	
98	SATHYA	47	F	YES	NO	NO	NO	NO	NO	CRYPTOGENIC	B	23	134	137	72.6	27.4	34	
99	RAJALINGAM	46	M	YES	NO	NO	YES	NO	NO	ALCOHOLIC	C	33	122	112	75.6	22.4	24	
100	NANDHAN	51	M	YES	YES	NO	NO	YES	NO	ALCOHOLIC	B	24	154	143	83.4	28.6	42	

101	KAMALAVENI	46	F	YES	NO	NO	YES	NO	NO	NASH	B	26	143	136	78.8	27.2	37	
102	KALIYAPAN	39	M	NO	YES	NO	NO	NO	NO	ALCOHOLIC	A	27	178	156	100.8	31.2	46	
103	SUBBATHAL	47	F	YES	NO	NO	YES	NO	NO	ALCOHOLIC	B	35	167	145	104	29	34	
104	MARATHAL	32	F	NO	YES	NO	NO	NO	NO	_	A	10	188	158	107.4	31.6	49	
105	JAYASEELAN	48	M	YES	NO	YES	YES	NO	NO	ALCOHOLIC	C	36	134	89	92.2	17.8	24	
106	MUTHAMMAL	43	F	NO	YES	NO	NO	NO	NO	_	A	23	176	125	98	25	53	
107	MANOJ	46	M	YES	YES	NO	NO	NO	NO	ALCOHOLIC	B	35	133	132	75.6	26.4	31	
108	KALA	53	F	NO	YES	NO	NO	NO	NO	_	A	22	167	137	94.6	27.4	45	
109	MUTHUSAMY	57	M	YES	NO	YES	NO	NO	NO	_	B	32	143	133	80.4	26.6	36	
110	PUSHPA	51	F	YES	NO	NO	YES	NO	NO	ALCOHOLIC	A	20	163	152	86.6	30.4	46	
111	TAMILARASAN	60	M	YES	NO	YES	YES	YES	NO	ALCOHOLIC	C	40	114	98	64.4	19.6	30	DEATH
112	VIGNESH	61	M	YES	NO	NO	NO	NO	NO	ALCOHOLIC	B	26	139	124	74.2	24.8	40	
113	MOHAMMED HANIFA	56	M	YES	NO	YES	NO	NO	NO	ALCOHOLIC	C	35	109	83	60.4	16.6	32	
114	DHANDAPANI	49	M	YES	NO	YES	NO	NO	NO	_	B	27	177	142	105.6	28.4	43	
115	MANIKKAM	46	M	YES	NO	NO	NO	NO	NO	ALCOHOLIC	A	18	187	154	102.2	30.8	54	
116	LIVINGSTON	36	M	YES	NO	NO	NO	NO	NO	_	B	28	164	132	96.6	26.4	41	
117	SOUNDARAJAN	45	M	YES	NO	NO	NO	NO	NO	ALCOHOLIC	B	32	136	121	73.8	24.2	38	
118	LAKSHMI	52	F	YES	NO	NO	NO	NO	NO	_	A	12	184	154	110.2	30.8	43	
119	NEELA	50	F	YES	YES	YES	NO	NO	NO	ALCOHOLIC	C	46	122	101	69.8	20.2	32	DEATH
120	SARAVANAN	39	M	YES	NO	NO	NO	NO	NO	ALCOHOLIC	B	10	143	123	85.4	24.6	33	